PI 1174528

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

May 25, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: *60/534,871*
FILING DATE: *January 08, 2004*
RELATED PCT APPLICATION NUMBER: *PCT/US04/08700*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. SIAS
Certifying Officer

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Attorney's Docket No. 046562/273014
Express Mail Label No. EV 390050519 US

PATENT

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Mail Stop Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. 1.53(c).

INVENTOR(s)

Name: Matthew Oliver Fraser
Residence: 408 Gablefield Lane
Apex, NC 27502

Name: Karl Bruce Thor
Residence: 109 Draymore Way
Morrisville, NC 27560

Name: Edward C. Burgard
Residence: 215 Cates Farm Road
Chapel Hill, NC 27516

Name: Lee R. Brettman
Residence: 183 Greystone Lane
Sudbury, MA 01776

Name: Steven B. Landau
Residence: 44 Tanglewood Road
Wellesley, MA 02481

Name: Daniel J. Ricca
Residence: 5855 Kiger Road
Rougemont, NC 27572

TITLE OF THE INVENTION *(500 characters maximum)*

METHODS FOR TREATING LOWER URINARY TRACT DISORDERS USING $\alpha_2\delta$ SUBUNIT CALCIUM CHANNEL MODULATORS WITH SMOOTH MUSCLE MODULATORS

CORRESPONDENCE ADDRESS

Edward R. Ergenzinger Jr.
Registration No. 47,549
Customer Number 00826
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Number of Pages 139)
- ☒ Drawing(s) (Figure 1 on pg. 81, Fig. 2 on pg. 82, Fig. 3 on pg. 83, Fig. 4 on pg. 84, Fig. 5 on pg. 85, Fig. 6 on pg. 86, Fig. 7 on pg. 87, Fig. 8 on pg. 92, Fig. 9 on pg. 93, Fig. 10 on pg. 94 of specification)
- ☐ Application Data Sheet. See 37 CFR 1.76
- ☐ CD(s), Number
- ☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES

- ☒ Applicant claims small entity status

- ☒ Check or money order is enclosed to cover the filing fee.
- ☐ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 16-0605.
- ☒ Please charge Deposit Account No. 16-0605 for any fee deficiency.

PROVISIONAL FILING FEE AMOUNT(s)

Large Entity $160.00
Small Entity $ 80.00

Filing Fee Amount: $80.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ☒ No.
- ☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Edward R. Ergenzinger Jr.
Registration No. 47,549
Date: January 8, 2004

CUSTOMER NO. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

"Express Mail" mailing label number EV 390050519 US
Date of Deposit January 8, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop Provisional Patent Application, Commissioner For Patents, Washington DC 20231.

Lynda-Jo Pixley

Attorney Docket No. 046562/273014

METHODS FOR TREATING LOWER URINARY TRACT DISORDERS USING $\alpha_2\delta$ SUBUNIT CALCIUM CHANNEL MODULATORS WITH SMOOTH MUSCLE MODULATORS

FIELD OF THE INVENTION

The invention relates to methods of using $\alpha_2\delta$ subunit calcium channel modulators, including gabapentin, pregabalin, GABA analogs, fused bicyclic or tricyclic amino acid analogs of gabapentin, amino acid compounds, and other compounds that interact with the $\alpha_2\delta$ calcium channel subunit, in combination with smooth muscle modulators for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients.

BACKGROUND OF THE INVENTION

Lower urinary tract disorders affect the quality of life of millions of men and women in the United States every year. Disorders of the lower urinary tract include overactive bladder, prostatitis and prostadynia, interstitial cystitis, benign prostatic hyperplasia, and, in spinal cord injured patients, spastic bladder.

Overactive bladder is a treatable medical condition that is estimated to affect 17 to 20 million people in the United States. Current treatments for overactive bladder include medication, diet modification, programs in bladder training, electrical stimulation, and surgery. Currently, antimuscarinics (which are subtypes of the general class of anticholinergics) are the primary medication used for the treatment of overactive bladder. This treatment suffers from limited efficacy and side effects such as dry mouth, dry eyes, dry vagina, palpitations, drowsiness, and constipation, which have proven difficult for some individuals to tolerate.

In recent years, it has been recognized among those of skill in the art that OAB can be divided into urgency without any demonstrable loss of urine as well as urgency with loss of urine. For example, a recent study examined the impact of all OAB symptoms on the quality of life of a community-based sample of the United States population. (Liberman *et al.* (2001) *Urology* 57: 1044-1050). This study demonstrated

that the group of individuals suffering from OAB without any demonstrable loss of urine have an impaired quality of life when compared with controls. Additionally, individuals with urgency alone have an impaired quality of life compared with controls.

Prostatitis and prostadynia are other lower urinary tract disorders that have been suggested to affect approximately 2-9% of the adult male population (Collins M M, *et al.*, (1998) *J. Urology*, 159: 1224-1228). Currently, there are no established treatments for prostatitis and prostadynia. Antibiotics are often prescribed, but with little evidence of efficacy. COX-2 selective inhibitors and α-adrenergic blockers and have been suggested as treatments, but their efficacy has not been established. Hot sitz baths and anticholinergic drugs have also been employed to provide some symptomatic relief.

Interstitial cystitis is another lower urinary tract disorder of unknown etiology that predominantly affects young and middle-aged females, although men and children can also be affected. Past treatments for interstitial cystitis have included the administration of antihistamines, sodium pentosanpolysulfate, dimethylsulfoxide, steroids, tricyclic antidepressants and narcotic antagonists, although these methods have generally been unsuccessful (Sant, G. R. (1989) Interstitial cystitis: pathophysiology, clinical evaluation and treatment. *Urology Annal* 3: 171-196).

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that is very common in men over 40 years of age. Invasive treatments for BPH include transurethral resection of the prostate, transurethral incision of the prostate, balloon dilation of the prostate, prostatic stents, microwave therapy, laser prostatectomy, transrectal high-intensity focused ultrasound therapy and transurethral needle ablation of the prostate. However, complications may arise through the use of some of these treatments, including retrograde ejaculation, impotence, postoperative urinary tract infection and some urinary incontinence. Non-invasive treatments for BPH include androgen deprivation therapy and the use of 5α-reductase inhibitors and α-adrenergic blockers. However, these treatments have proven only minimally to moderately effective for some patients.

Lower urinary tract disorders are particularly problematic for individuals suffering from spinal cord injury. Following spinal cord injury, the bladder is usually affected in one of two ways: 1) "spastic" or "reflex" bladder, in which the bladder fills

with urine and a reflex automatically triggers the bladder to empty; or 2) "flaccid" or "non-reflex" bladder, in which the reflexes of the bladder muscles are absent or slowed. Treatment options for these disorders usually include intermittent catheterization, indwelling catheterization, or condom catheterization, but these methods are invasive and frequently inconvenient. Urinary sphincter muscles may also be affected by spinal cord injuries, resulting in an inability of urinary sphincter muscles to relax when the bladder contracts ("dyssynergia"). Traditional treatments for dyssynergia include medications that have been somewhat inconsistent in their efficacy or surgery.

Because existing therapies and treatments for lower urinary tract disorders in normal and spinal cord injured patients are associated with limitations as described above, new therapies and treatments are therefore desirable.

SUMMARY OF THE INVENTION

Compositions and methods for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients are provided. Compositions of the invention comprise $\alpha_2\delta$ subunit calcium channel modulators in combination with one or more compounds with smooth muscle modulatory effects. According to the present invention, $\alpha_2\delta$ subunit calcium channel modulators include gabapentin, pregabalin, GABA analogs, fused bicyclic or tricyclic amino acid analogs of gabapentin, and amino acid compounds. Compounds with smooth muscle modulatory effects include antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. Compositions of the invention include combinations of the aforementioned compounds as well as pharmaceutically acceptable, pharmacologically active salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof.

The compositions are administered in therapeutically effective amounts to a patient in need thereof for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. It is recognized that the compositions may be administered by any means of administration as long as an effective amount for the treatment of painful and non-painful symptoms associated with lower urinary tract

disorders in normal and spinal cord injured patients is delivered. The compositions may be formulated, for example, for sustained, continuous, or as-needed administration.

DETAILED DESCRIPTION OF THE INVENTION

Overview and Definitions

The present invention provides compositions and methods for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. The lower urinary tract disorders of the present invention include, but are not limited to such disorders as painful and non-painful overactive bladder, prostatitis and prostadynia, interstitial cystitis, benign prostatic hyperplasia, and, in spinal cord injured patients, spastic bladder. The compositions comprise a therapeutically effective dose of an $\alpha_2\delta$ subunit calcium channel modulator, including gabapentin and pregabalin, in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics, (particularly those that do not have an amine embedded in an 8-azabicyclo[3.2.1]octan-3-ol skeleton), β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. The methods are accomplished by administering, for example, various compositions and formulations that contain quantities of an $\alpha_2\delta$ subunit calcium channel modulator and/or other compounds that interact with $\alpha_2\delta$ subunit-containing calcium channels in combination with one or more compounds with smooth muscle modulatory effects.

The present invention now will be described more fully hereinafter with reference to the accompanying drawings, in which some, but not all embodiments of the invention are shown. Indeed, these inventions may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Like numbers refer to like elements throughout.

Many modifications and other embodiments of the inventions set forth herein will come to mind to one skilled in the art to which these inventions pertain having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the inventions are not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be

included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

It must be noted that as used in this specification and the appended embodiments, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well as two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

By "non-painful" is intended sensations or symptoms including mild or general discomfort that a patient subjectively describes as not producing or resulting in pain.

By "painful" is intended sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

By "lower urinary tract" is intended all parts of the urinary system except the kidneys. By "lower urinary tract disorder" is intended any disorder involving the lower urinary tract, including but not limited to overactive bladder, prostatitis, interstitial cystitis, benign prostatic hyperplasia, and spastic and flaccid bladder. By "non-painful lower urinary tract disorder" is intended any lower urinary tract disorder involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. By "painful lower urinary tract disorder" is intended any lower urinary tract disorder involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

By "bladder disorder" is intended any condition involving the urinary bladder. By "non-painful bladder disorder" is intended any bladder disorder involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. By "painful bladder disorder" is intended any bladder disorder involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

By "overactive bladder"or "OAB" is intended any form of lower urinary tract disorder characterized by increased frequency of micturition or the desire to void, whether complete or episodic, and where loss of voluntary control ranges from partial to

total and whether there is loss of urine (incontinence) or not. By "painful overactive bladder" is intended any form of overactive bladder, as defined above, involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain. By "non-painful overactive bladder" is intended any form of overactive bladder, as defined above, involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. Non-painful symptoms can include, but are not limited to, urinary urgency, incontinence, urge incontinence, stress incontinence, urinary frequency, and nocturia.

"OAB wet" is used herein to describe overactive bladder in patients with incontinence, while "OAB dry" is used herein to describe overactive bladder in patients without incontinence.

By "urinary urgency" is intended sudden strong urges to urinate with little or no chance to postpone the urination. By "incontinence" is meant the inability to control excretory functions, including urination (urinary incontinence). By "urge incontinence" or "urinary urge incontinence" is intended the involuntary loss of urine associated with an abrupt and strong desire to void. By "stress incontinence" or "urinary stress incontinence" is intended a medical condition in which urine leaks when a person coughs, sneezes, laughs, exercises, lifts heavy objects, or does anything that puts pressure on the bladder. By "urinary frequency" is intended urinating more frequently than the patient desires. As there is considerable interpersonal variation in the number of times in a day that an individual would normally expect to urinate, "more frequently than the patient desires" is further defined as a greater number of times per day than that patient's historical baseline. "Historical baseline" is further defined as the median number of times the patient urinated per day during a normal or desirable time period. By "nocturia" is intended being awakened from sleep to urinate more frequently than the patient desires.

By "neurogenic bladder" or "neurogenic overactive bladder" is intended overactive bladder as described further herein that occurs as the result of neurological damage due to disorders including but not limited to stroke, Parkinson's disease, diabetes, multiple sclerosis, peripheral neuropathy, or spinal cord lesions.

By "detrusor hyperreflexia" is intended a condition characterized by uninhibited detrusor, wherein the patient has some sort of neurologic impairment. By "detrusor instability" or "unstable detrusor" is intended conditions where there is no neurologic abnormality.

By "prostatitis" is intended any type of disorder associated with an inflammation of the prostate, including chronic bacterial prostatitis and chronic non-bacterial prostatitis. By "non-painful prostatitis" is intended prostatitis involving sensations or symptoms, including mild or general discomfort, that a patient subjectively describes as not producing or resulting in pain. By "painful prostatitis" is intended prostatitis involving sensations or symptoms that a patient subjectively describes as producing or resulting in pain.

"Chronic bacterial prostatitis" is used in its conventional sense to refer to a disorder associated with symptoms that include inflammation of the prostate and positive bacterial cultures of urine and prostatic secretions. "Chronic non-bacterial prostatitis" is used in its conventional sense to refer to a disorder associated with symptoms that include inflammation of the prostate and negative bacterial cultures of urine and prostatic secretions. "Prostadynia" is used in its conventional sense to refer to a disorder generally associated with painful symptoms of chronic non-bacterial prostatitis as defined above, without inflammation of the prostate. "Interstitial cystitis" is used in its conventional sense to refer to a disorder associated with symptoms that include irritative voiding symptoms, urinary frequency, urgency, nocturia, and suprapubic or pelvic pain related to and relieved by voiding.

"Benign prostatic hyperplasia" is used in its conventional sense to refer to a disorder associated with benign enlargement of the prostate gland.

"Spastic bladder" or "reflex bladder" is used in its conventional sense to refer to a condition following spinal cord injury in which bladder emptying has become unpredictable.

"Flaccid bladder" or "non-reflex bladder" is used in its conventional sense to refer to a condition following spinal cord injury in which the reflexes of the bladder muscles are absent or slowed.

"Dyssynergia" is used in its conventional sense to refer to a condition following spinal cord injury in which patients characterized by an inability of urinary sphincter muscles to relax when the bladder contracts.

"Vulvodynia" is used in its conventional sense to refer to a condition characterized by gynecologic syndrome characterized by unexplained vulvar pain, sexual dysfunction, and psychological disability.

"Vulvar vestibulitis" (also known as "vulvar vestibulitis syndrome," "focal vulvitis," and "vestibular adenitis") is used in its conventional sense to refer to a condition that is a subtype of vulvodynia characterized by: 1) pain on vestibular touch or attempted vaginal entry; 2) tenderness to Q-tip pressure localized within the vulvar vestibule; 3) physical findings confined to vestibular erythema of various degrees; and 4) an exclusion of other causes for vestibular erythema and tenderness, such as candidiasis (yeast infections) or herpes infections. Other symptoms may include itching, swelling and excoriation.

The terms "active agent" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical compound that induces a desired effect, i.e., in this case, treatment of painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. The primary active agents herein are $\alpha_2\delta$ subunit calcium channel modulators and/or smooth muscle relaxants. The present invention comprises a combination therapy wherein an $\alpha_2\delta$ subunit calcium channel modulator is administered with one or more smooth muscle modulator. Such combination therapy may be carried out by administration of the different active agents in a single composition, by concurrent administration of the different active agents in different compositions, or by sequential administration of the different active agents. Included are derivatives and analogs of those compounds or classes of compounds specifically mentioned that also induce the desired effect.

The term "$\alpha_2\delta$ subunit calcium channel modulator" as used herein refers to an agent that is capable of interacting with the $\alpha_2\delta$ subunit of a calcium channel, including a binding event, including subtypes of the $\alpha_2\delta$ calcium channel subunit as disclosed in Klugbauer et al. (1999) *J. Neurosci.*19: 684-691, to produce a physiological effect, such as opening, closing, blocking, up-regulating functional expression, down-regulating

functional expression, or desensitization, of the channel. Unless otherwise indicated, the term "$\alpha_2\delta$ subunit calcium channel modulator" is intended to include gabapentin, pregabalin, GABA analogs, fused bicyclic or tricyclic amino acid analogs of gabapentin, amino acid compounds, and other compounds that interact with the $\alpha_2\delta$ calcium channel subunit as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "peptidomimetic" is used in its conventional sense to refer to a molecule that mimics the biological activity of a peptide but is no longer peptidic in chemical nature, including molecules that lack amide bonds between amino acids, as well as pseudo-peptides, semi-peptides and peptoids. Peptidomimetics according to this invention provide a spatial arrangement of reactive chemical moieties that closely resembles the three-dimensional arrangement of active groups in the peptide on which the peptidomimetic is based. As a result of this similar active-site geometry, the peptidomimetic has effects on biological systems that are similar to the biological activity of the peptide.

The term "smooth muscle modulator" as used herein refers to any compound that inhibits or blocks the contraction of smooth muscles, including but not limited to antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. Smooth muscle modulators can be "direct" (also known as "musculotropic") or "indirect" (also known as "neurotropic"). "Direct smooth muscle modulators" are smooth muscle modulators that act by inhibiting or blocking contractile mechanisms within smooth muscle, including but not limited to modification of the interaction between actin and myosin. "Indirect smooth muscle modulators" are smooth muscle modulators that act by inhibiting or blocking neurotransmission that results in the contraction of smooth muscle, including but not limited to blockade of presynaptic facilitation of acetylcholine release at the axon terminal of motor neurons terminating in smooth muscle.

The term "anticholinergic agent" as used herein refers to any acetylcholine receptor antagonist, including antagonists of nicotinic and/or muscarinic acetylcholine

receptors. The term "antinicotinic agent" as used herein is intended any nicotinic acytylcholine receptor antagonist. The term "antimuscarinic agent" as used herein is intended any muscarinic acetylcholine receptor antagonist. Unless otherwise indicated, the terms "anticholinergic agent," "antinicotinic agent," and "antimuscarinic agent" are intended to include anticholinergic, antinicotinic, and antimuscarinic agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "β3 adrenergic agonist" is used in its conventional sense to refer to a compound that binds to and agonizes β3 adrenergic receptors. Unless otherwise indicated, the term "β3 adrenergic agonist" is intended to include β3 adrenergic agonist agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "spasmolytic" (also known as "antispasmodic") is used in its conventional sense to refer to a compound that relieves or prevents muscle spasms, especially of smooth muscle. Unless otherwise indicated, the term "spasmolytic" is intended to include spasmolytic agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "neurokinin receptor antagonist" is used in its conventional sense to refer to a compound that binds to and antagonizes neurokinin receptors. Unless otherwise indicated, the term "neurokinin receptor antagonist" is intended to include neurokinin receptor antagonist agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "bradykinin receptor antagonist" is used in its conventional sense to refer to a compound that binds to and antagonizes bradykinin receptors. Unless otherwise indicated, the term "bradykinin receptor antagonist" is intended to include bradykinin receptor antagonist agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The term "nitric oxide donor" is used in its conventional sense to refer to a compound that releases free nitric oxide when administered to a patient. Unless otherwise indicated, the term "nitric oxide donor" is intended to include nitric oxide donor agents as disclosed further herein, as well as salts, esters, amides, prodrugs, active metabolites, and other derivatives thereof. Further, it is understood that any salts, esters, amides, prodrugs, active metabolites or other derivatives are pharmaceutically acceptable as well as pharmacologically active.

The terms "treating" and "treatment" as used herein refer to relieving the painful or non-painful symptoms or other clinically observed sequelae for clinically diagnosed disorders as described herein, including disorders associated with lower urinary tract in normal and spinal cord injured patients.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, i.e., relieving the painful and non-painful symptoms associated with lower urinary tract disorders in normal and spinal cord injured patients, as explained above. It is recognized that the effective amount of a drug or pharmacologically active agent will vary depending on the route of administration, the selected compound, and the species to which the drug or pharmacologically active agent is administered. It is also recognized that one of skill in the art will determine appropriate effective amounts by taking into account such factors as metabolism, bioavailability, and other factors that affect plasma levels of a drug or pharmacologically active agent following administration within the unit dose ranges disclosed further herein for different routes of administration.

By "pharmaceutically acceptable," such as in the recitation of a "pharmaceutically acceptable carrier," or a "pharmaceutically acceptable acid addition salt," is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. "Pharmacologically active" (or simply "active") as in a "pharmacologically active" derivative or metabolite, refers to a derivative or metabolite having the same type of pharmacological activity as the parent compound. When the term "pharmaceutically acceptable" is used to refer to a derivative (e.g., a salt or an analog) of an active agent, it is to be understood that the compound is pharmacologically active as well, i.e., therapeutically effective for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients.

By "continuous" dosing is meant the chronic administration of a selected active agent.

By "as-needed" dosing, also known as "*pro re nata*" "prn" dosing, and "on demand" dosing or administration is meant the administration of a single dose of the active agent at some time prior to commencement of an activity wherein suppression of the painful and non-painful symptoms of a lower urinary tract disorder in normal and spinal cord injured patients, would be desirable. Administration can be immediately prior to such an activity, including about 0 minutes, about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, or about 10 hours prior to such an activity, depending on the formulation.

By "short-term" is intended any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes after drug administration.

By "rapid-offset" is intended any period of time up to and including about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2

hours, about 1 hour, about 40 minutes, about 20 minutes, or about 10 minutes after drug administration.

The term "controlled release" is intended to refer to any drug-containing formulation in which release of the drug is not immediate, i.e., with a "controlled release" formulation, oral administration does not result in immediate release of the drug into an absorption pool. The term is used interchangeably with "non-immediate release" as defined in Remington: The Science and Practice of Pharmacy, Twentieth Ed. (Philadelphia, Pa.: Lippincott Williams & Wilkins, 2000).

The "absorption pool" represents a solution of the drug administered at a particular absorption site, and k_r, k_a, and k_e are first-order rate constants for: 1) release of the drug from the formulation; 2) absorption; and 3) elimination, respectively. For immediate release dosage forms, the rate constant for drug release k_r is far greater than the absorption rate constant k_a. For controlled release formulations, the opposite is true, i.e., $k_r <<< k_a$, such that the rate of release of drug from the dosage form is the rate-limiting step in the delivery of the drug to the target area. The term "controlled release" as used herein includes any nonimmediate release formulation, including but not limited to sustained release, delayed release and pulsatile release formulations.

The term "sustained release" is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period such as up to about 72 hours, about 66 hours, about 60 hours, about 54 hours, about 48 hours, about 42 hours, about 36 hours, about 30 hours, about 24 hours, about 18 hours, about 12 hours, about 10 hours, about 8 hours, about 7 hours, about 6 hours, about 5 hours, about 4 hours, about 3 hours, about 2 hours, or about 1 hour after drug administration.

The term "delayed release" is used in its conventional sense to refer to a drug formulation that provides for an initial release of the drug after some delay following drug administration and that preferably, although not necessarily, includes a delay of up to about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours.

The term "pulsatile release" is used in its conventional sense to refer to a drug formulation that provides release of the drug in such a way as to produce pulsed plasma profiles of the drug after drug administration. The term "immediate release" is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

The term "immediate release" is used in its conventional sense to refer to a drug formulation that provides for release of the drug immediately after drug administration.

By the term "transdermal" drug delivery is meant delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream.

The term "topical administration" is used in its conventional sense to mean delivery of a topical drug or pharmacologically active agent to the skin or mucosa.

The term "oral administration" is used in its conventional sense to mean delivery of a drug through the mouth and ingestion through the stomach and digestive tract.

The term "inhalation administration" is used in its conventional sense to mean delivery of an aerosolized form of the drug by passage through the nose or mouth during inhalation and passage of the drug through the walls of the lungs.

The term "intravesical administration" is used in its conventional sense to mean delivery of a drug directly into the bladder.

By the term "parenteral" drug delivery is meant delivery by passage of a drug into the blood stream without first having to pass through the alimentary canal, or digestive tract. Parenteral drug delivery may be "subcutaneous," referring to delivery of a drug by administration under the skin. Another form of parenteral drug delivery is "intramuscular," referring to delivery of a drug by administration into muscle tissue. Another form of parenteral drug delivery is "intradermal," referring to delivery of a drug by administration into the skin. An additional form of parenteral drug delivery is "intravenous," referring to delivery of a drug by administration into a vein. An additional form of parenteral drug delivery is "intra-arterial," referring to delivery of a drug by administration into an artery. Another form of parenteral drug delivery is "transdermal," referring to delivery of a drug by passage of the drug through the skin and into the bloodstream. Another form of parenteral drug delivery is "intrathecal," referring to

delivery of a drug directly into the into the intrathecal space (where fluid flows around the spinal cord).

Still another form of parenteral drug delivery is "transmucosal," referring to administration of a drug to the mucosal surface of an individual so that the drug passes through the mucosal tissue and into the individual's blood stream. Transmucosal drug delivery may be "buccal" or "transbuccal," referring to delivery of a drug by passage through an individual's buccal mucosa and into the bloodstream. Another form of transmucosal drug delivery herein is "lingual" drug delivery, which refers to delivery of a drug by passage of a drug through an individual's lingual mucosa and into the bloodstream. Another form of transmucosal drug delivery herein is "sublingual" drug delivery, which refers to delivery of a drug by passage of a drug through an individual's sublingual mucosa and into the bloodstream. Another form of transmucosal drug delivery is "nasal" or "intranasal" drug delivery, referring to delivery of a drug through an individual's nasal mucosa and into the bloodstream. An additional form of transmucosal drug delivery herein is "rectal" or "transrectal" drug delivery, referring to delivery of a drug by passage of a drug through an individual's rectal mucosa and into the bloodstream. Another form of transmucosal drug delivery is "urethral" or "transurethral" delivery, referring to delivery of the drug into the urethra such that the drug contacts and passes through the wall of the urethra. An additional form of transmucosal drug delivery is "vaginal" or "transvaginal" delivery, referring to delivery of a drug by passage of a drug through an individual's vaginal mucosa and into the bloodstream. An additional form of transmucosal drug delivery is "perivaginal" delivery, referring to delivery of a drug through the vaginolabial tissue into the bloodstream.

In order to carry out the method of the invention, a selected active agent is administered to a patient suffering from a painful or non-painful lower urinary tract disorder in normal and spinal cord injured patients. A therapeutically effective amount of the active agent may be administered orally, intravenously, subcutaneously, transmucosally (including buccally, sublingually, transurethrally, and rectally), topically, transdermally, by inhalation, intravesically, intrathecally or using any other route of administration.

Lower Urinary Tract Disorders

Lower urinary tract disorders affect the quality of life of millions of men and women in the United States every year. While the kidneys filter blood and produce urine, the lower urinary tract is concerned with storage and elimination of this waste liquid and includes all other parts of the urinary tract except the kidneys. Generally, the lower urinary tract includes the ureters, the urinary bladder, and the urethra. Disorders of the lower urinary tract include painful and non-painful overactive bladder, prostatitis and prostadynia, interstitial cystitis, benign prostatic hyperplasia, and, in spinal cord injured patients, spastic bladder and flaccid bladder.

Overactive bladder is a treatable medical condition that is estimated to affect 17 to 20 million people in the United States. Symptoms of overactive bladder include urinary frequency, urgency, nocturia (the disturbance of nighttime sleep because of the need to urinate) and urge incontinence (accidental loss of urine) due to a sudden and unstoppable need to urinate. As opposed to stress incontinence, in which loss of urine is associated with physical actions such as coughing, sneezing, exercising, or the like, urge incontinence is usually associated with an overactive detrusor muscle (the smooth muscle of the bladder which contracts and causes it to empty).

There is no single etiology for overactive bladder. Neurogenic overactive bladder (or neurogenic bladder) occurs as the result of neurological damage due to disorders such as stroke, Parkinson's disease, diabetes, multiple sclerosis, peripheral neuropathy, or spinal cord lesions. In these cases, the overactivity of the detrusor muscle is termed detrusor hyperreflexia. By contrast, non-neurogenic overactive bladder can result from non-neurological abnormalities including bladder stones, muscle disease, urinary tract infection or drug side effects.

Due to the enormous complexity of micturition (the act of urination) the exact mechanism causing overactive bladder is unknown. Overactive bladder may result from hypersensitivity of sensory neurons of the urinary bladder, arising from various factors including inflammatory conditions, hormonal imbalances, and prostate hypertrophy. Destruction of the sensory nerve fibers, either from a crushing injury to the sacral region of the spinal cord, or from a disease that causes damage to the dorsal root fibers as they enter the spinal cord may also lead to overactive bladder. In addition, damage to the

spinal cord or brain stem causing interruption of transmitted signals may lead to abnormalities in micturition. Therefore, both peripheral and central mechanisms may be involved in mediating the altered activity in overactive bladder.

In spite of the uncertainty regarding whether central or peripheral mechanisms, or both, are involved in overactive bladder, many proposed mechanisms implicate neurons and pathways that mediate non-painful visceral sensation. Pain is the perception of an aversive or unpleasant sensation and may arise through a variety of proposed mechanisms. These mechanisms include activation of specialized sensory receptors that provide information about tissue damage (nociceptive pain), or through nerve damage from diseases such as diabetes, trauma or toxic doses of drugs (neuropathic pain) (See, e.g., A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.; Benevento *et al.* (2002) *Physical Therapy Journal* 82:601-12). Nociception may give rise to pain, but not all stimuli that activate nociceptors are experienced as pain (A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.). Somatosensory information from the bladder is relayed by nociceptive Aδ and C fibers that enter the spinal cord via the dorsal root ganglion (DRG) and project to the brainstem and thalamus via second or third order neurons (Andersson (2002) *Urology* 59:18-24; Andersson (2002) *Urology* 59:43-50; Morrison, J., Steers, W.D., Brading, A., Blok, B., Fry, C., de Groat, W.C., Kakizaki, H., Levin, R., and Thor, K.B., "Basic Urological Sciences" In: Incontinence (vol. 2) Abrams, P. Khoury, S., and Wein, A. (Eds.) Health Publications, Ltd., Plymbridge Ditributors, Ltd., Plymouth, UK., (2002). A number of different subtypes of sensory afferent neurons may be involved in neurotransmission from the lower urinary tract. These may be classified as, but not limited to, small diameter, medium diameter, large diameter, myelinated, unmyelinated, sacral, lumbar, peptidergic, non-peptidergic, IB4 positive, IB4 negative, C fiber, Aδ fiber, high threshold or low threshold neurons. Nociceptive input to the DRG is thought to be conveyed to the brain along several ascending pathways, including the spinothalamic, spinoreticular, spinomesencephalic, spinocervical, and in some cases dorsal column/medial lemniscal tracts (A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.). Central mechanisms, which are not fully understood, are thought to convert some, but not

all, nociceptive information into painful sensory perception (A.I. Basbaum and T.M. Jessell (2000) The perception of pain. In *Principles of Neural Science*, 4th. ed.).

Current treatments for overactive bladder include medication, diet modification, programs in bladder training, electrical stimulation, and surgery. Currently, antimuscarinics (which are subtypes of the general class of anticholinergics) are the primary medication used for the treatment of overactive bladder. This treatment suffers from limited efficacy and side effects such as dry mouth, dry eyes, dry vagina, palpitations, drowsiness, and constipation, which have proven difficult for some individuals to tolerate.

Although many compounds have been explored as treatments for disorders involving pain of the bladder or other pelvic visceral organs, relatively little work has been directed toward treatment of non-painful sensory symptoms associated with bladder disorders such as overactive bladder. Current treatments for overactive bladder include medication, diet modification, programs in bladder training, electrical stimulation, and surgery. Currently, antimuscarinics (which are subtypes of the general class of anticholinergics) are the primary medication used for the treatment of overactive bladder. This treatment suffers from limited efficacy and side effects such as dry mouth, dry eyes, dry vagina, palpitations, drowsiness, and constipation, which have proven difficult for some individuals to tolerate.

While the use of gabapentin, pregabalin, and GABA analogs have been suggested as possible treatments for incontinence (see, e.g., WO00/061135), overactive bladder (or OAB) can occur with or without incontinence. In recent years, it has been recognized among those of skill in the art that the cardinal symptom of OAB is urgency without regard to any demonstrable loss of urine. For example, a recent study examined the impact of all OAB symptoms on the quality of life of a community-based sample of the United States population. (Liberman *et al.* (2001) *Urology* 57: 1044-1050). This study demonstrated that individuals suffering from OAB without any demonstrable loss of urine have an impaired quality of life when compared with controls. Additionally, individuals with urgency alone have an impaired quality of life compared with controls.

Although urgency is now believed to be the primary symptom of OAB, to date it has not been evaluated in a quantified way in clinical studies. Corresponding to this new

understanding of OAB, however, the terms OAB Wet (with incontinence) and OAB Dry (without incontinence) have been proposed to describe these different patient populations (see, e.g., WO03/051354). The prevalence of OAB Wet and OAB Dry is reported to be similar in men and women, with a prevalence rate in the United States of 16.6% (Stewart *et al.*, "Prevalence of Overactive Bladder in the United States: Results from the NOBLE Program," Abstract Presented at the *Second International Consultation on Incontinence*, July 2001, Paris, France).

Prostatitis and prostadynia are other lower urinary tract disorders that have been suggested to affect approximately 2-9% of the adult male population (Collins M M, et al., (1998) "How common is prostatitis? A national survey of physician visits," *Journal of Urology*, 159: 1224-1228). Prostatitis is associated with an inflammation of the prostate, and may be subdivided into chronic bacterial prostatitis and chronic non-bacterial prostatitis. Chronic bacterial prostatitis is thought to arise from bacterial infection and is generally associated with such symptoms as inflammation of the prostate, the presence of white blood cells in prostatic fluid, and/or pain. Chronic non-bacterial prostatitis is an inflammatory and painful condition of unknown etiology characterized by excessive inflammatory cells in prostatic secretions despite a lack of documented urinary tract infections, and negative bacterial cultures of urine and prostatic secretions. Prostadynia (chronic pelvic pain syndrome) is a condition associated with the painful symptoms of chronic non-bacterial prostatitis without an inflammation of the prostate.

Currently, there are no established treatments for prostatitis and prostadynia. Antibiotics are often prescribed, but with little evidence of efficacy. COX-2 selective inhibitors and α-adrenergic blockers and have been suggested as treatments, but their efficacy has not been established. Hot sitz baths and anticholinergic drugs have also been employed to provide some symptomatic relief.

Interstitial cystitis is another lower urinary tract disorder of unknown etiology that predominantly affects young and middle-aged females, although men and children can also be affected. Symptoms of interstitial cystitis may include irritative voiding symptoms, urinary frequency, urgency, nocturia and suprapubic or pelvic pain related to and relieved by voiding. Many interstitial cystitis patients also experience headaches as

well as gastrointestinal and skin problems. In some extreme cases, interstitial cystitis may also be associated with ulcers or scars of the bladder.

Past treatments for interstitial cystitis have included the administration of antihistamines, sodium pentosanpolysulfate, dimethylsulfoxide, steroids, tricyclic antidepressants and narcotic antagonists, although these methods have generally been unsuccessful (Sant, G. R. (1989) Interstitial cystitis: pathophysiology, clinical evaluation and treatment. *Urology Annal* 3: 171-196).

Benign prostatic hyperplasia (BPH) is a non-malignant enlargement of the prostate that is very common in men over 40 years of age. BPH is thought to be due to excessive cellular growth of both glandular and stromal elements of the prostate. Symptoms of BPH include urinary frequency, urge incontinence, nocturia, and reduced urinary force and speed of flow.

Invasive treatments for BPH include transurethral resection of the prostate, transurethral incision of the prostate, balloon dilation of the prostate, prostatic stents, microwave therapy, laser prostatectomy, transrectal high-intensity focused ultrasound therapy and transurethral needle ablation of the prostate. However, complications may arise through the use of some of these treatments, including retrograde ejaculation, impotence, postoperative urinary tract infection and some urinary incontinence. Non-invasive treatments for BPH include androgen deprivation therapy and the use of 5α-reductase inhibitors and α-adrenergic blockers. However, these treatments have proven only minimally to moderately effective for some patients.

Lower urinary tract disorders are particularly problematic for individuals suffering from spinal cord injury. After spinal cord injury, the kidneys continue to make urine, and urine can continue to flow through the ureters and urethra because they are the subject of involuntary neural and muscular control, with the exception of conditions where bladder to smooth muscle dyssenergia is present. By contrast, bladder and sphincter muscles are also subject to voluntary neural and muscular control, meaning that descending input from the brain through the spinal cord drives bladder and sphincter muscles to completely empty the bladder. Following spinal cord injury, such descending input may be disrupted such that individuals may no longer have voluntary control of their bladder and sphincter muscles. Spinal cord injuries can also disrupt sensory signals

that ascend to the brain, preventing such individuals from being able to feel the urge to urinate when their bladder is full.

Following spinal cord injury, the bladder is usually affected in one of two ways. The first is a condition called "spastic" or "reflex" bladder, in which the bladder fills with urine and a reflex automatically triggers the bladder to empty. This usually occurs when the injury is above the T12 level. Individuals with spastic bladder are unable to determine when, or if, the bladder will empty. The second is "flaccid" or "non-reflex" bladder, in which the reflexes of the bladder muscles are absent or slowed. This usually occurs when the injury is below the T12/L1 level. Individuals with flaccid bladder may experience over-distended or stretched bladders and "reflux" of urine through the ureters into the kidneys. Treatment options for these disorders usually include intermittent catheterization, indwelling catheterization, or condom catheterization, but these methods are invasive and frequently inconvenient.

Urinary sphincter muscles may also be affected by spinal cord injuries, resulting in a condition known as "dyssynergia." Dyssynergia involves an inability of urinary sphincter muscles to relax when the bladder contracts, including active contraction in response to bladder contraction, which prevents urine from flowing through the urethra and results in the incomplete emptying of the bladder and "reflux" of urine into the kidneys. Traditional treatments for dyssynergia include medications that have been somewhat inconsistent in their efficacy or surgery.

Vulvodynia and Vulvar Vestibulitis

In addition to the lower urinary tract disorders described above, the related genitourinary tract disorders vulvodynia and vulvar vestibulitis have been etiologically and pathologically linked to such lower urinary tract disorders as interstitial cystitis (*See* Selo-Ojeme *et al.* (2002) *Int. Urogynecol. J. Pelvic Floor Dysfunction* 13: 261-2; Metts (2001) *Am. Fam. Physician* 64: 1199-206; Wesselmann (2001) *World J. Urol.* 19: 180-5; Parsons *et al.* (2001) *Obstet. Gynecol.* 98: 127-32; Heim (2001) *Am. Fam. Physician* 63: 1535-44; Stewart *et al.* (1997) *J. Reprod. Med.* 42: 131-4; Fitzpatrick *et al.* (1993) *Obstet. Gynecol.* 81: 860-2). Vulvar vestibulitis syndrome (herein "vulvar vestibulitis") is a subtype of vulvodynia. Vulvodynia is a complex gynecologic syndrome characterized by

unexplained vulvar pain, sexual dysfunction, and psychological disability. Although the exact prevalence of vulvodynia is unknown, the condition is relatively common. It has been estimated that 1.5 million American women may suffer from some degree of vulvodynia.

The most common subtype of vulvodynia is vulvar vestibulitis (also called "focal vulvitis" and "vestibular adenitis"). Vulvar vestibulitis presents a constellation of symptoms involving and limited to the vulvar vestibule. The criteria for recognizing vulvar vestibulitis include: 1) pain on vestibular touch or attempted vaginal entry; 2) tenderness to Q-tip pressure localized within the vulvar vestibule; 3) physical findings confined to vestibular erythema of various degrees; and 4) an exclusion of other causes for vestibular erythema and tenderness, such as candidiasis (yeast infections) or herpes infections. Other symptoms include itching, swelling and excoriation.

The pain in vulvar vestibulitis may be described as sharp, burning, or a sensation of rawness. In severe cases, dyspareunia (recurrent or persistent genital pain associated with sexual intercourse) totally prohibits sexual intercourse. Pain may also be elicited on tampon insertion, biking, or wearing tight pants. The erythema may be diffuse or focal, and may be localized around the orifices of the vestibular glands or at the fourchette. In addition, patient symptoms may often include itching. Morbidities extend well beyond the local symptoms, with many women undergoing tremendous changes in psychosexual self-image, and can include profound adverse effects on marriages and other important relationships.

Vulvar vestibulitis may be acute or chronic. In one study, an arbitrary cutoff of three months of symptoms was used to distinguish between the acute and chronic forms (Marinoff and Turner, Am. J. Obstet. Gynecol. 165:1228-33, 1991). Most clinicians use an arbitrary cutoff of six months to distinguish between the acute and chronic forms. Some investigators have attempted to find a common histopathological aspect to vulvar vestibulitis, but have failed to do so (Pyka *et al.* (1988) *Int. J. Gynecol. Pathol.* 7: 249-57).

The causes of vulvar vestibulitis are multifactorial. Known and suspected causes of the acute form include fungal or bacterial infection (e.g. Candida, Trichomonas), chemical irritants (e.g. soaps, douches, sprays), therapeutic agents (e.g. antiseptics,

suppositories, creams, 5-fluorouracil methods (e.g. cryosurgery, laser treatment), and allergic drug reactions. In the acute form, treatment of the presumed cause may lead to rapid relief.

Vulvar vestibulitis may become chronic if the cause becomes persistent or recurrent and may persist long after all suspected causes have been treated. Many causes of chronic vulvar vestibulitis are of unknown etiology. Although no direct cause and effect relationship has been shown, it has been suggested that oxalates in the urine, altered vaginal pH, localized peripheral neuropathy, and subclinical viral infections can all contribute to the syndrome. A history of fungal infection is present in most patients who have vulvar vestibulitis, suggesting that recurrent yeast infections may somehow play a role in the initiation of the syndrome. It has been suggested that conditions such as recurrent candidiasis may lead to local changes in the vaginal immune system, including both Th1 and Th2 type responses (Fidel and Sobel, Clin. Microbiol. Reviews 9(3):335-48, 1996).

Because of its multiple causes, and its frequently unknown causes, vulvar vestibulitis can be very difficult to treat. The first-line therapy for vulvar vestibulitis is the treatment of its suspected causes. This includes the pharmacologic treatment of infections and the discontinued use of the irritants and therapeutic agents, local and systemic, that may contribute to the problem. Topical anesthetics, corticosteroids, and sex hormones may provide some symptomatic relief. Further treatments may include dietary modifications, physical therapy and biofeedback, use of topical, oral, or injected therapeutic agents, or surgery. Unfortunately, no single treatment works in all patients. Moreover, many of these approaches involve complex medical procedures, significant costs, and/or undesirable side effects.

Given their relationship to the lower urinary tract disorders described elsewhere herein, the compositions and methods of the present invention are also expected to be useful for treating vulvodynia and/or vulvar vestibulitis. The compositions would comprise a therapeutically effective dose of an $\alpha_2\delta$ subunit calcium channel modulator, including gabapentin and pregabalin, in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics (particularly those that do not have an amine embedded in an 8-azabicyclo[3.2.1]octan-3-ol skeleton), β3 adrenergic

agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. The methods would be accomplished by administering, for example, various compositions and formulations that contain quantities of an $\alpha_2\delta$ subunit calcium channel modulator and/or other compounds that interact with $\alpha_2\delta$ subunit-containing calcium channels in combination with one or more compounds with smooth muscle modulatory effects to treat vulvodynia and/or vulvar vestibulitis.

Peripheral vs. Central Effects

The mammalian nervous system comprises a central nervous system (CNS, comprising the brain and spinal cord) and a peripheral nervous system (PNS, comprising sympathetic, parasympathetic, sensory, motor, and enteric neurons outside of the brain and spinal cord). Where an active agent according to the present invention is intended to act centrally (i.e., exert its effects via action on neurons in the CNS), the active agent must either be administered directly into the CNS or be capable of bypassing or crossing the blood-brain barrier. The blood-brain barrier is a capillary wall structure that effectively screens out all but selected categories of substances present in the blood, preventing their passage into the CNS. The unique morphologic characteristics of the brain capillaries that make up the blood-brain barrier are: 1) epithelial-like high resistance tight junctions which literally cement all endothelia of brain capillaries together within the blood-brain barrier regions of the CNS; and 2) scanty pinocytosis or transendothelial channels, which are abundant in endothelia of peripheral organs. Due to the unique characteristics of the blood-brain barrier, hydrophilic drugs and peptides that readily gain access to other tissues in the body are barred from entry into the brain or their rates of entry are very low.

The blood-brain barrier can be bypassed effectively by direct infusion of the active agent into the brain, or by intranasal administration or inhalation of formulations suitable for uptake and retrograde transport of the active agent by olfactory neurons. The most common procedure for administration directly into the CNS is the implantation of a catheter into the ventricular system or intrathecal space. Alternatively, the active agent can be modified to enhance its transport across the blood-brain barrier. This generally requires some solubility of the drug in lipids, or other appropriate modification

known to one of skill in the art. For example, the active agent may be truncated, derivatized, latentiated (converted from a hydrophilic drug into a lipid-soluble drug), conjugated to a lipophilic moiety or to a substance that is actively transported across the blood-brain barrier, or modified using standard means known to those skilled in the art. See, for example, Pardridge, Endocrine Reviews 7: 314-330 (1986) and U.S. Pat. No. 4,801,575.

Where an active agent according to the present invention is intended to act exclusively peripherally (i.e., exert its effects via action either on neurons in the PNS or directly on target tissues), it may be desirable to modify the compounds of the present invention such that they will not pass the blood-brain barrier. The principle of blood-brain barrier permeability can therefore be used to design active agents with selective potency for peripheral targets. Generally, a lipid-insoluble drug will not cross the blood-brain barrier, and will not produce effects on the CNS. A basic drug that acts on the nervous system may be altered to produce a selective peripheral effect by quaternization of the drug, which decreases its lipid solubility and makes it virtually unavailable for transfer to the CNS. For example, the charged antimuscarinic drug methscopalamine bromide has peripheral effects while the uncharged antimuscarinic drug scopolamine acts centrally. One of skill in the art can select and modify active agents of the present invention using well-known standard chemical synthetic techniques to add a lipid impermeable functional group such a quaternary amine, sulfate, carboxylate, phosphate, or sulfonium to prevent transport across the blood-brain barrier. Such modifications are by no means the only way in which active agents of the present invention may be modified to be impermeable to the blood-brain barrier; other well known pharmaceutical techniques exist and would be considered to fall within the scope of the present invention.

Calcium Channels

Voltage gated calcium channels, also known as voltage dependent calcium channels, are multi-subunit membrane-spanning proteins which permit controlled calcium influx from an extracellular environment into the interior of a cell. Opening and closing (gating) of voltage gated calcium channels is controlled by a voltage sensitive

region of the protein containing charged amino acids that move within an electric field. The movement of these charged groups leads to conformational changes in the structure of the channel resulting in conducting (open/activated) or non-conducting (closed/inactivated) states.

Voltage gated calcium channels are present in a variety of tissues and are implicated in several vital processes in animals. Changes in calcium influx into cells mediated through these calcium channels have been implicated in various human diseases such as epilepsy, stroke, brain trauma, Alzheimer's disease, multi-infarct dementia, other classes of dementia, Korsakoff's disease, neuropathy caused by a viral infection of the brain or spinal cord (e.g., human immunodeficiency viruses, etc.), amyotrophic lateral sclerosis, convulsions, seizures, Huntington's disease, amnesia, or damage to the nervous system resulting from reduced oxygen supply, poison, or other toxic substances (See, e.g., U.S. Pat. No. 5,312,928).

Voltage gated calcium channels have been classified by their electrophysiological and pharmacological properties as T, L, N, P and Q types (for reviews see McCleskey *et al.* (1991) *Curr. Topics Membr.* 39:295-326; and Dunlap *et al.* (1995) *Trends. Neurosci.* 18:89-98). Because there is some overlap in the biophysical properties of the high voltage-activated channels, pharmacological profiles are useful to further distinguish them. L-type channels are sensitive to dihydropyridine agonists and antagonists. N-type channels are blocked by the peptides ω-conotoxin GVIA and ω-conotoxin MVIIA, peptide toxins from the cone shell mollusks, *Conus geographus* and *Conus magus*, respectively. P-type channels are blocked by the peptide ω-agatoxin IVA from the venom of the funnel web spider, *Agelenopsis aperta*, although some studies have suggested that ω-agatoxin IVA also blocks N-type channels (Sidach at al. (2000) *J. Neurosci.* 20: 7174-82). A fourth type of high voltage-activated calcium channel (Q-type) has been described, although whether the Q- and P-type channels are distinct molecular entities is controversial (Sather *et al.*(1995) *Neuron* 11:291-303; Stea *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:10576-10580; Bourinet *et al.* (1999) *Nature Neuroscience* 2:407-415).

Voltage gated calcium channels are primarily defined by the combination of different subunits: α_1, α_2, β, γ, and δ (see Caterall (2000) *Annu. Rev. Cell. Dev. Biol.* 16:

521-55). Ten types of α_1 subunits, four complexes, four β subunits, and two γ subunits are known (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; see also Klugbauer et al. (1999) *J. Neurosci.*19: 684-691).

Based upon the combination of different subunits, calcium channels may be divided into three structurally and functionally related families: Ca_v1, Ca_v2, and Ca_v3 (for reviews, see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Ertel *et al.* (2000) *Neuron* 25: 533-55). L-type currents are mediated by a Ca_v1 family of α_1 subunits (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra). Ca_v2 channels form a distinct family with less than 40% amino acid sequence identity with $Ca_v1\alpha_1$ subunits (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra). Cloned $Ca_v2.1$ subunits conduct P- or Q-type currents that are inhibited by ω-agatoxin IVA (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Sather *et al.* (1993) *Neuron* 11: 291-303; Stea *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91: 10576-80; Bourinet *et al.* (1999) *Nat. Neurosci.* 2: 407-15). $Ca_v2.2$ subunits conduct N-type calcium currents and have a high affinity for ω-conotoxin GVIA, ω-conotoxin MVIIA, and synthetic versions of these peptides including Ziconotide (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Dubel *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:5058-62; Williams *et al.* (1992) *Science* 257: 389-95). Cloned $Ca_v2.3$ subunits conduct a calcium current known as R-type and are resistant to organic antagonists specific for L-type calcium currents and peptide toxins specific for N-type or P/Q-type currents (see Caterall, *Annu. Rev. Cell. Dev. Biol.*, supra; Randall *et al.* (1995) *J. Neurosci.* 15: 2995-3012; Soong *et al.* (1994) *Science* 260: 1133-36; Zhang *et al.* (1993) *Neuropharmacology* 32: 1075-88).

Acetylcholine Receptors

Acetylcholine is a chemical neurotransmitter in the nervous systems of all animals. "Cholinergic neurotransmission" refers to neurotransmission that involves acetylcholine, and has been implicated in the control of functions as diverse as locomotion, digestion, cardiac rate, "fight or flight" responses, and learning and memory (Salvaterra (Feb. 2000) Acetylcholine. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, http:/www.els.net). Receptors for acetylcholine are classified into two general categories based on the plant alkaloids that preferentially interact with them: 1)

nicotinic (nicotine binding); or 2) muscarinic (muscarine binding) (See, e.g., Salvaterra, Acetylcholine, supra).

The two general categories of acetylcholine receptors may be further divided into subclasses based upon differences in their pharmacological and electrophysiological properties. For example, nicotinic receptors are composed of a variety of subunits that are used to identify the following subclasses: 1) muscle nicotinic acetylcholine receptors; 2) neuronal nicotinic acetylcholine receptors that do not bind the snake venom α-bungarotoxin; and 3) neuronal nicotinic acetylcholine receptors that do bind the snake venom α-bungarotoxin (Dani et al. (July 1999) Nicotinic Acetylcholine Receptors in Neurons. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, http:/www.els.net; Lindstrom (October 2001) Nicotinic Acetylcholine Receptors. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, http:/www.els.net). By contrast, muscarinic receptors may be divided into five subclasses, labeled M_1-M_5, and preferentially couple with specific G-proteins (M_1, M_3, and M_5 with G_q; M_2 and M_4 with G_i/G_o) (Nathanson (July 1999) Muscarinic Acetylcholine Receptors. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, http:/www.els.net). In general, muscarinic receptors have been implicated in bladder function (See, e.g., Appell (2002) *Cleve. Clin. J. Med.* 69: 761-9; Diouf et al. (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9; Crandall (2001) *J. Womens Health Gend. Based Med.* 10: 735-43; Chapple (2000) *Urology* 55: 33-46).

Adrenergic Receptors

Adrenergic receptors are cell-surface receptors for two major catecholamine hormones and neurotransmitters: noradrenaline and adrenaline. (Malbon et al. (Feb. 2000) Adrenergic Receptors. In *Encyclopedia of Life Sciences*. London: Nature Publishing Group, http:/www.els.net). Adrenergic receptors have been implicated in critical physiological processes, including blood pressure control, myocardial and smooth muscle contractility, pulmonary function, metabolism, and central nervous system activity (See, e.g., Malbon et al., Adrenergic Receptors, supra). Two classes of adrenergic receptors have been identified, α and β, that may be further subdivided into three major families (α1, α2, and β), each with at least three subtypes (α1A, B, and, D;

α_2A, B, and C; and β1, β2, and β3) based upon their binding characteristics to different agonists and molecular cloning techniques. (See, e.g., Malbon et al., Adrenergic Receptors, supra). It has been shown that β3 adrenergic receptors are expressed in the detrusor muscle, and that the detrusor muscle relaxes with a β3-agonist (Takeda, M. *et al.* (1999) *J.Pharmacol.Exp.Ther.* 288: 1367-1373), and in general, β3 adrenergic receptors have been implicated in bladder function (See, e.g., Takeda *et al.* (2002) *Neuourol. Urodyn.* 21: 558-65; Takeda *et al.* (2000) *J. Pharmacol. Exp. Ther.* 293: 939-45.

Spasmolytics

Spasmolytics are compounds that relieve or prevent muscle spasms, especially of smooth muscle. In general, spasmolytics have been implicated as having efficacy in the treatment of bladder disorders (See. e.g., Takeda *et al.* (2000) *J. Pharmacol. Exp. Ther.* 293: 939-45).

Neurokinin Receptors

Tachykinins (TKs) are a family of structurally related peptides that include substance P, neurokinin A (NKA) and neurokinin B (NKB). Neurons are the major source of TKs in the periphery. An important general effect of TKs is neuronal stimulation, but other effects include endothelium-dependent vasodilation, plasma protein extravasation, mast cell recruitment and degranulation and stimulation of inflammatory cells (See Maggi, C. A. (1991) *Gen. Pharmacol.*, 22: 1-24). In general, tachykinin receptors have been implicated in bladder function (See, e.g., Kamo *et al.* (2000) *Eur. J. Pharmacol.* 401: 235-40 and Omhura *et al.* (1997) *Urol. Int.* 59: 221-5).

Substance P activates the neurokinin receptor subtype referred to as NK_1. Substance P is an undecapeptide that is present in sensory nerve terminals. Substance P is known to have multiple actions that produce inflammation and pain in the periphery after C-fiber activation, including vasodilation, plasma extravasation and degranulation of mast cells (Levine, J. D. *et. al.* (1993) *J. Neurosci.* 13: 2273).

Neurokinin A is a peptide which is colocalized in sensory neurons with substance P and which also promotes inflammation and pain. Neurokinin A activates the *specific neurokinin* receptor referred to as NK_2 (Edmonds-Alt, S., *et. al.* (1992) *Life Sci.* 50:

PL101). In the urinary tract, TKs are powerful spasmogens acting through only the NK_2 receptor in the human bladder, as well as the human urethra and ureter (Maggi, C. A. (1991) *Gen. Pharmacol.*, 22: 1-24).

Bradykinin Receptors

Bradykinin receptors generally are divided into bradykinin$_1$ (B_1) and bradykinin$_2$ (B_2) subtypes. Studies have shown that acute peripheral pain and inflammation produced by bradykinin are mediated by the B_2 subtype whereas bradykinin-induced pain in the setting of chronic inflammation is mediated via the B_1 subtype (Perkins, M. N., *et. al.* (1993) *Pain* 53: 191-97); Dray, A., *et. al.* (1993) *Trends Neurosci.* 16: 99-104). In general, bradykinin receptors have been implicated in bladder function (See, e.g., Meini *et al.* (2000) *Eur. J. Pharmacol.* 388: 177-82 and Belichard *et al.* (1999) *Br. J. Pharmacol.* 128: 213-9).

Nitric Oxide

Nitric oxide donors may be included in the present invention particularly for their anti-spasm activity. Nitric oxide (NO) plays a critical role as a molecular mediator of many physiological processes, including vasodilation and regulation of normal vascular tone. The action of NO is implicated in intrinsic local vasodilation mechanisms. NO is the smallest biologically active molecule known and is the mediator of an extraordinary range of physiological processes (Nathan (1994) *Cell* 78: 915-918; Thomas (1997) *Neurosurg. Focus* 3: Article 3). NO is also a known physiologic antagonist of endothelin-1, which is the most potent known mammalian vasoconstrictor, having at least ten times the vasoconstrictor potency of angiotensin II (Yanagisawa *et al.* (1988) *Nature* 332: 411-415; Kasuya *et al.* (1993) *J. Neurosurg.* 79: 892-898; Kobayashi *et al.*, (1991) *Neurosurgery* 28: 673-679). The biological half-life of NO is extremely short (Morris *et al.* (1994) *Am. J. Physiol.* 266: E829-E839; Nathan (1994) *Cell* 78: 915-918). NO accounts entirely for the biological effects of endothelium-derived relaxing factor (EDRF) and is an extremely potent vasodilator that is believed to work through the action of cGMP-dependent protein kinases to effect vasodilation (Henry *et al.* (1993) *FASEB J.* 7: 1124-1134; Nathan (1992) *FASEB J.* 6: 3051-3064; Palmer *et al.*, (1987) *Nature* 327:

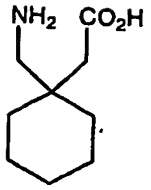
524-526; Snyder *et al.* (1992) *Scientific American* 266: 68-77).

Within endothelial cells, an enzyme known as NO synthase (NOS) catalyzes the conversion of L-arginine to NO which acts as a diffusible second messenger and mediates responses in adjacent smooth muscle cells. NO is continuously formed and released by the vascular endothelium under basal conditions which inhibits contractions and controls basal coronary tone and is produced in the endothelium in response to various agonists (such as acetylcholine) and other endothelium dependent vasodilators. Thus, regulation of NOS activity and the resultant levels of NO are key molecular targets controlling vascular tone (Muramatsu *et. al.* (1994) *Coron. Artery Dis.* 5: 815-820).

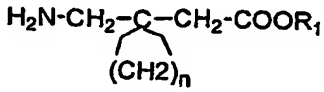
Agents

Gamma-aminobutyric acid (GABA) analogs are compounds that are derived from or based on GABA. GABA analogs are either readily available or readily synthesized using methodologies known to those of skill in the art. Exemplary GABA analogs and their salts include gabapentin and pregabalin, and any other GABA analogs as described in U.S. Pat. No. 4,024,175, U.S. Pat. No. 5,563,175, U.S. Patent No. 6,316,638, PCT Publication No. WO 93/23383, Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845, and Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177, which are hereby incorporated by reference. Agents useful in the practice of the invention also include those disclosed in U.S. Application No. 20020111338, cyclic amino acid compounds as disclosed in PCT Publication No. WO 99/08670, compositions disclosed in PCT Publication No. WO 99/08670, U.S. Patent No. 6,342,529, controlled release formulations as disclosed in U.S. Application No. 20020119197 and U.S. Patent No. 5,955,103, and sustained release compounds and formulations as disclosed in PCT Publication No. WO 02/28411, PCT Publication No. WO 02/28881, PCT Publication No. WO 02/28883, PCT Publication No. WO 02/32376, PCT Publication No. WO 02/42414, U.S. Application No. 20020107208, U.S. Application No. 20020151529, and U.S. Application No. 20020098999.

Gabapentin (Neurontin, or 1-(aminomethyl) cyclohexaneacetic acid) is an anticonvulsant drug with a high binding affinity for some calcium channel subunits, and is represented by the following structure:



Gabapentin is one of a series of compounds of formula:



in which R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6. Although gabapentin was originally developed as a GABA-mimetic compound to treat spasticity, gabapentin has no direct GABAergic action and does not block GABA uptake or metabolism. (For review, see Rose *et al.* (2002) *Analgesia* 57:451-462). Gabapentin has been found, however, to be an effective treatment for the prevention of partial seizures in patients who are refractory to other anticonvulsant agents (Chadwick (1991) *Gabapentin*, In Pedley T A, Meldrum B S (eds.), *Recent Advances in Epilepsy*, Churchill Livingstone, New York, pp. 211-222). Gabapentin and the related drug pregabalin may interact with the $\alpha_2\delta$ subunit of calcium channels (Gee *et al.* (1996) *J. Biol. Chem.* 271: 5768-5776).

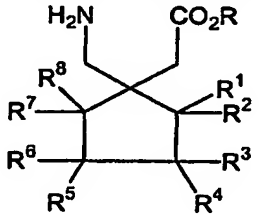
In addition to its known anticonvulsant effects, gabapentin has been shown to block the tonic phase of nociception induced by formalin and carrageenan, and exerts an inhibitory effect in neuropathic pain models of mechanical hyperalgesia and mechanical/thermal allodynia (Rose *et al.* (2002) *Analgesia* 57: 451-462). Double-blind, placebo-controlled trials have indicated that gabapentin is an effective treatment for painful symptoms associated with diabetic peripheral neuropathy, post-herpetic neuralgia, and neuropathic pain (see, e.g., Backonja *et al.* (1998) *JAMA* 280:1831-1836; Mellegers *et al.* (2001) *Clin. J. Pain* 17:284-95).

Pregabalin, (S)-(3-aminomethyl)-5-methylhexanoic acid or (S)-isobutyl GABA, is another GABA analog whose use as an anticonvulsant has been explored (Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845). Pregabalin has been shown to possess even higher binding affinity for the $\alpha_2\delta$ subunit of calcium channels than gabapentin (Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177).

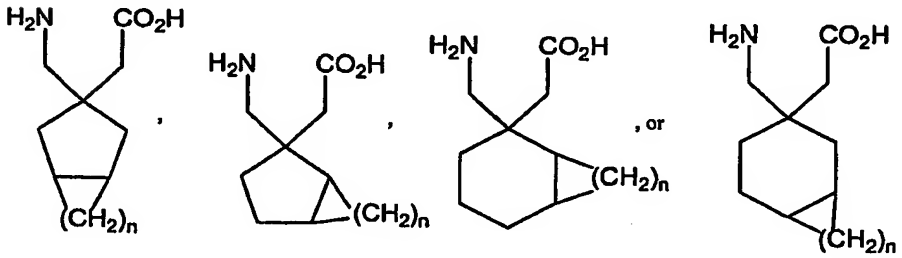
Other GABA analogs which display binding affinity to the $\alpha_2\delta$ subunit of calcium channels include, without limitation, cis-(1S,3R)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, cis-(1R,3S)-(1-(aminomethyl)-3-methylcyclohexane)acetic acid, 1α,3α,5α-(1-aminomethyl)-(3,5-dimethylcyclohexane)acetic acid, (9-(aminomethyl)bicyclo[3.3.1]non-9-yl)acetic acid, and (7-(aminomethyl)bicyclo[2.2.1]hept-7-yl)acetic acid (Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845; Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177).

Fused bicyclic or tricyclic amino acid analogs of gabapentin have also been identified that are useful in the present invention. Such compounds include, for example:

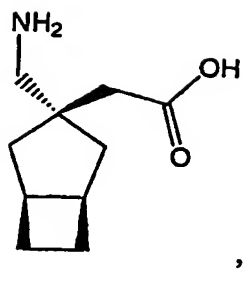
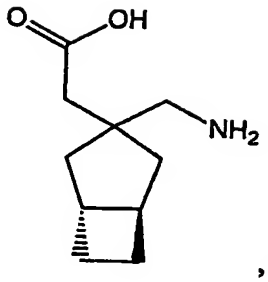
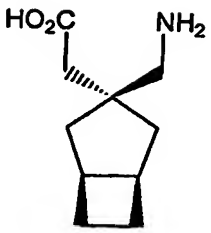
1. Cyclic amino acids (illustrated below) as disclosed in PCT Publication No. WO99/21824 and derivatives and analogs thereof;



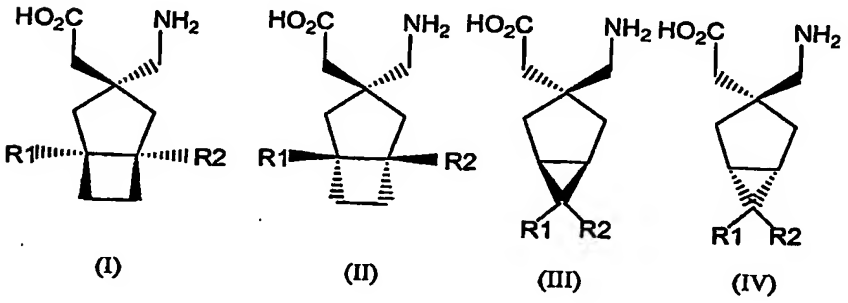
2. Bicyclic amino acids (illustrated below) as disclosed in published U.S. Patent Application No. 60/160725, including those disclosed as having high activity as measured in a radioligand binding assay using [3H]gabapentin and the $\alpha_2\delta$ subunit derived from porcine brain tissue; and

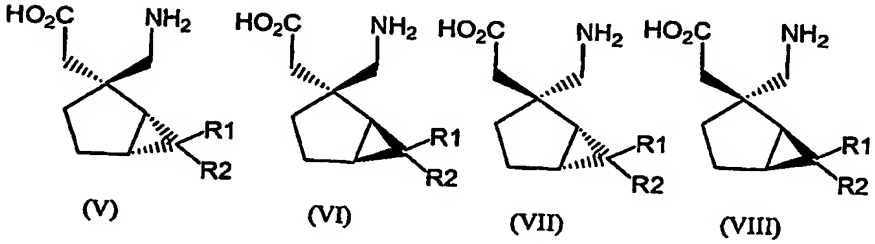


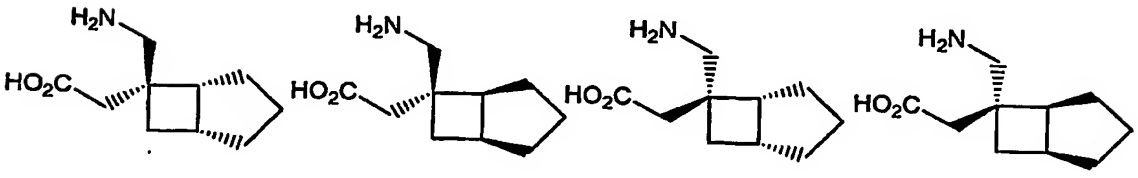
I II III IV

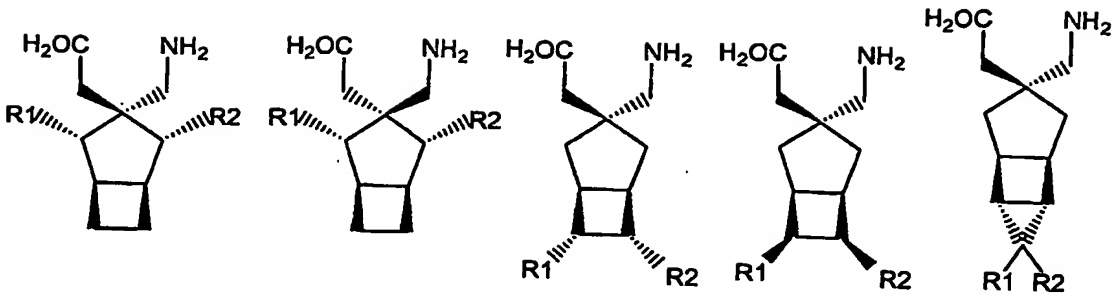


, or


3. Bicyclic amino acid analogs (illustrated below) as disclosed in UK Patent Application GB 2 374 595 and derivatives and analogs thereof.

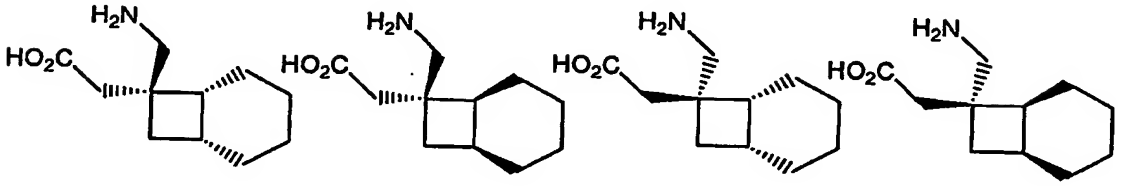

(I) (II) (III) (IV)


(V) (VI) (VII) (VIII)

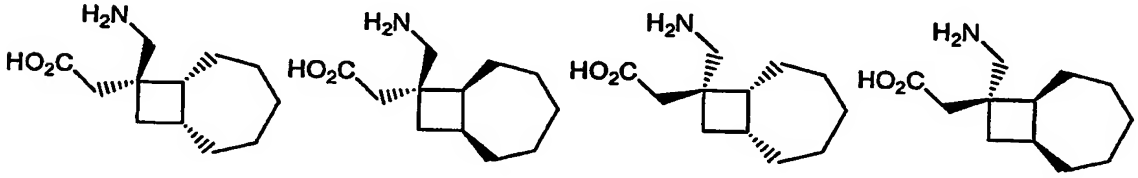

(IX) (X) (XI) (XII)



(XIII) (XIV) (XV) (XVI) (XVII)



(XVIII) (XIX) (XX) (XXI)



(XXI) (XXII) (XXIII) (XXIV)

Other agents useful in the present invention include any compound that binds to the $\alpha_2\delta$ subunit of a calcium channel. Compounds that have been identified as modulators of calcium channels include, but are not limited to those described in US Patent No. 6,316,638, US Patent No. 6,492,375, US Patent No. 6,294,533, US Patent No. 6,011,035, US Patent No. 6,387,897, US Patent No. 6,310,059, US Patent No. 6,294,533, US Patent No. 6,267,945, PCT Publication No. WO01/49670, PCT Publication No. WO01/46166, and PCT Publication No. WO01/45709. The identification of which of these compounds have a binding affinity for the $\alpha_2\delta$ subunit of calcium channels can be determined by performing $\alpha_2\delta$ binding affinity studies as described by Gee *et al.* (Gee *et al.* (1996) *J. Biol. Chem.* 271:5768-5776). The identification of still further compounds, including other GABA analogs, that have a binding affinity for the $\alpha_2\delta$ subunit of calcium

channels can also be determined by performing $\alpha_2\delta$ binding affinity studies as described by Gee *et al.* (Gee *et al.* (1996) *J. Biol. Chem.* 271:5768-5776).

Other agents useful in the present invention include any anticholinergic agent, specifically, any antimuscarinic agent Compounds that have been identified as antimuscarinic agents and are useful in the present invention include, but are not limited to:

a. Darifenacin (Daryon®);
b. Solifenacin;
c. YM-905 (solifenacin succinate);
d. Solifenacin monohydrochloride;
e. Oxybutynin (Ditropan®);
f. S-Oxybutynin;
g. N-desethyl-oxybutynin;
h. tolterodine (Detrol®);
i. Propiverine (Detrunorm®);
j. Propantheline bromide (Pro-Banthine®);
k. Hyoscyamine sulfate (Levsin®, Cystospaz®);
l. Dicyclomine hydrochloride (Bentyl®);
m. Flavoxate hydrochloride (Urispas®);
n. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
o. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;
p. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;
q. alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol proprionate;
r. 1-methyl-4-piperidyl diphenylpropoxyacetate;
s. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;

t. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;

u. pirenzipine;

v. methoctramine;

w. 4-diphenylacetoxy-N-methyl piperidine methiodide;

x. tropicamide;

y. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and

z. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine).

The identification of further compounds that have antimuscarinic activity and would therefore be useful in the present invention can be determined by performing muscarinic receptor binding specificity studies as described by Nilvebrant (2002) *Pharmacol. Toxicol.* 90: 260-7 or cystometry studies as described by Modiri *et al.* (2002) *Urology* 59: 963-8.

Other agents useful in the present invention include any β3 adrenergic agonist agent. Compounds that have been identified as β3 adrenergic agonist agents and are useful in the present invention include, but are not limited to:

a. TT-138 and phenylethanolamine compounds as disclosed in US Patent No. 6,069,176, PCT Publication No. WO 97/15549 and available from Mitsubishi Pharma Corp.;

b. FR-149174 and propanolamine derivatives as disclosed in US Patent Nos. 6,495,546 and 6,391,915 and available from Fujisawa Pharmaceutical Co.;

c. KUC-7483, available from Kissei Pharmaceutical Co.,

d. 4'-hydroxynorephedrine derivatives such as 2- 2-chloro-4-(2-((1S,2R)-2-hydroxy-2-(4-hydroxyphenyl)-1-methylethylamino)ethyl)phenoxy acetic acid as disclosed in Tanaka *et al.* (2003) *J. Med. Chem.* 46: 105-12;

e. 2-amino-1-phenylethanol compounds, such as BRL35135 ((R*R*)-(.+-.)-[4-[2-[2-(3-chlorophenyl)-2-ydroxyethylamino]propyl]phenox y]acetic acid methyl ester hydrobromide salt as disclosed in Japanese Patent Publication No. 26744 of 1988 and European Patent Publication No. 23385), and SR58611A ((RS)-N-(7-ethoxycarbonylmethoxy-1,2,3,4-tetrahydronaphth-2-yl)-2-(3-chlor ophenyl)-2-hydroxyethanamine hydrochloride as disclosed in Japanese Laid-open Patent Publication No. 66152 of 1989 and European Laid-open Patent Publication No. 255415);

f. GS 332 (Sodium (2R)-[3-[3-[2-(3 Chlorophenyl)-2-hydroxyethylamino]cyclohexyl]phenoxy]acetate) as disclosed in Iizuka *et al.* (1998) *J. Smooth Muscle Res.* 34: 139-49;

g. BRL-37,344 (4-[-[(2-hydroxy-(3-chlorophenyl) ethyl)-amino]propyl]phenoxyacetate) as disclosed in Tsujii *et al.* (1998) *Physiol. Behav.* 63: 723-8 and available from Glaxosmithkline;

h. BRL-26830A as disclosed in Takahashi *et al.* (1992) *Jpn Circ. J.* 56: 936-42 and available from Glaxosmithkline;

i. CGP 12177 (4-[3-t-butylamino-2-hydroxypropoxy]benzimidazol-2- one) (a β1/β2 adrenergic antagonist reported to act as an agonist for the β3 adrenergic receptor) as described in Tavernier *et al.* (1992) J. Pharmacol. Exp. Ther. 263: 1083-90 and available from Ciba-Geigy;

j. CL 316243 (R,R-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3- benzodioxole-2,2-dicarboxylate) as disclosed in Berlan *et al.* (1994) *J. Pharmacol. Exp. Ther.* 268: 1444-51;

k. Compounds having β3 adrenergic agonist activity as disclosed in US Patent Application 20030018061;

l. ICI 215,001 HCl ((*S*)-4-[2-Hydroxy-3-phenoxypropylaminoethoxy]phenoxyacetic acid hydrochloride) as disclosed in Howe (1993) *Drugs Future* 18: 529 and available from AstraZeneca/ICI Labs;

m. ZD 7114 HCl (ICI D7114; (*S*)-4-[2-Hydroxy-3-phenoxypropylaminoethoxy]-*N*-(2-methoxyethyl)phenoxyacetamide HCl) as disclosed in Howe (1993) *Drugs Future* 18: 529 and available from AstraZeneca/ICI Labs;

n. Pindolol (1-(1*H*-Indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol) as disclosed in Blin *et al* (1994) *Mol.Pharmacol.* 44: 1094;

o. (*S*)-(-)-Pindolol ((*S*)-1-(1*H*-indol-4-yloxy)-3-[(1-methylethyl)amino]-2-propanol) as disclosed in Walter *et al* (1984) *Naunyn-Schmied.Arch.Pharmacol.* 327: 159 and Kalkman (1989) *Eur.J.Pharmacol.* 173: 121;

p. SR 59230A HCl (1-(2-Ethylphenoxy)-3-[[(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]amino]-(2*S*)-2-propanol hydrochloride) as disclosed in Manara *et al.* (1995) *Pharmacol. Comm.* 6: 253 and Manara *et al.* (1996) *Br. J. Pharmacol.* 117: 435 and available from Sanofi-Midy; and

q. SR 58611 (*N*[2s)7-carb-ethoxymethoxy-1,2,3,4-tetra-hydronaphth]-(2r)-2-hydroxy-2(3-chlorophenyl) ethamine hydrochloride) as disclosed in Gauthier *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290: 687-693 and available from Sanofi Research.

The identification of further compounds that have β3 adrenergic agonist activity and would therefore be useful in the present invention can be determined by performing radioligand binding assays and/or contractility studies as described by Zilberfarb *et al.* (1997) *J. Cell Sci.* 110: 801-807; Takeda *et al.* (1999) *J. Pharmacol. Exp. Ther.* 288: 1367-1373; and Gauthier *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290: 687-693.

Other agents useful in the present invention include any spasmolytic agent. Compounds that have been identified as spasmolytic agents and are useful in the present invention include, but are not limited to:

a. α-α-diphenylacetic acid-4-(N-methyl-piperidyl) esters as disclosed in US Patent No. 5,897,875;

b. Human and porcine spasmolytic polypeptides in glycosylated form and variants thereof as disclosed in US Patent No. 5,783,416;

c. Dioxazocine derivatives as disclosed in US Patent No. 4,965,259;

d. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylnorscopine ethers as disclosed in US Patent No. 4,608,377;

e. Quaternary salts of dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones as disclosed in US Patent No. 4,594,190;

f. Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts as disclosed in US Patent No. 4,558,054;

g. Pancreatic spasmolytic polypeptides as disclosed in US Patent No. 4,370,317;

h. Triazinones as disclosed in US Patent No. 4,203,983;

i. 2-(4-Biphenylyl)-N-(2-diethylamino alkyl)propionamide as disclosed in US Patent No. 4,185,124;

j. Piperazino-pyrimidines as disclosed in US Patent No. 4,166,852;

k. Aralkylamino carboxylic acids as disclosed in US Patent No. 4,163,060;

l. Aralkylamino sulfones as disclosed in US Patent No. 4,034,103;

m. Smooth muscle spasmolytic agents as disclosed in US Patent No. 6,207,852; and

n. papaverine.

The identification of further compounds that have spasmolytic activity and would therefore be useful in the present invention can be determined by performing bladder strip contractility studies as described in US Patent No. 6,207,852; Noronha-Blob *et al.* (1991) *J. Pharmacol. Exp. Ther.*256: 562-567; and/or Kachur *et al.* (1988) *J. Pharmacol. Exp. Ther.*247: 867-872.

Other agents useful in the present invention include any neurokinin receptor antagonist agent. Suitable neurokinin receptor antagonists for use in the present invention that act on the NK_1 receptor include, but are not limited to: 1-imino-2-(2-methoxy-phenyl)-ethyl)-7,7-diphenyl-4-perhydroisoindolone(3aR ,7aR) ("RP 67580"); 2S,3S-cis-3-(2-methoxybenzylamino)-2-benzhydrylquinuclidine ("CP 96,345"); and (aR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10, 11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g] [1,7]naphthyridine-6,13-dione)("TAK-637"). Suitable neurokinin receptor antagonists for use in the present invention that act on the NK_2 receptor include but are not limited to: ((S)-N-methyl-N-4-(4-acetylamino-4-phenylpiperidino)-2-(3,4-dichloropheny l)butylbenzamide ("SR 48968"); Met-Asp-Trp-Phe-Dap-Leu ("MEN 10,627"); and cyc(Gln-Trp-Phe-Gly-Leu-Met) ("L 659,877"). The identification of further compounds that have neurokinin receptor antagonist activity and would therefore be useful in the present invention can be determined by performing binding assay studies as described in Hopkins *et al.* (1991) *Biochem. Biophys. Res. Comm.* 180: 1110-1117; and Aharony *et al.* (1994) Mol. Pharmacol. 45: 9-19.

Other agents useful in the present invention include any bradykinin receptor antagonist agent. Suitable bradykinin receptor antagonists for use in the present invention that act on the B_1 receptor include but are not limited to: des-arg^{10}HOE 140 (available from Hoechst Pharmaceuticals) and des-Arg^{9}bradykinin (DABK). Suitable bradykinin receptor antagonists for use in the present invention that act on the B_2 receptor include but are not limited to: D-Phe^7-BK; D-Arg-(Hyp^3 -Thi^{5,8} -D-Phe^7)-BK ("NPC 349"); D-Arg-(Hyp^3-D-Phe^7)-BK ("NPC 567"); D-Arg-(Hyp^3 -Thi^5 -D-Tic^7 -Oic^8)-BK

("HOE 140"); H-DArg-Arg-Pro-Hyp-Gly-Thi-c(Dab-DTic-Oic-Arg)c(7gamma-10alpha)("MEN11270"); H-DArg-Arg-Pro-Hyp-Gly-Thi-Ser-DTic-Oic-Arg-OH("Icatibant"); (E)-3-(6-acetamido-3-pyridyl)-N-[N-[2, 4-dichloro-3-[(2-methyl-8-quinolinyl) oxymethyl] phenyl]-N-methylaminocarbonylmethyl]acrylamide ("FR173567"); and WIN 64338.

These compounds are more fully described in Perkins, M. N., *et. al.*, *Pain, supra*; Dray, A., *et. al.*, *Trends Neurosci., supra*; and Meini *et al.* (2000) *Eur. J. Pharmacol.* 388: 177-82. The identification of further compounds that have bradykinin receptor antagonist activity and would therefore be useful in the present invention can be determined by performing binding assay studies as described in Manning *et al.* (1986) *J. Pharmacol. Exp. Ther.* 237: 504 and US Patent No. 5,686,565.

Other agents useful in the present invention include any nitric oxide donor agent. Suitable nitric oxide donors for the practice of the present invention include but are not limited to:

a. Nitroglycerin;
b. Sodium nitroprusside;
c. FK 409 (NOR-3);
d. FR 144420 (NOR-4);
e. 3-morpholinosydnonimine;
f. Linsidomine chlorohydrate ("SIN-1");
g. S-nitroso-N-acetylpenicillamine ("SNAP");
h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
i. NCX 4016 (available from NicOx S.A.);
j. NCX 701 (available from NicOx S.A.);
k. NCX 1022 (available from NicOx S.A.);
l. HCT 1026 (available from NicOx S.A.);
m. NCX 1015 (available from NicOx S.A.);
n. NCX 950 (available from NicOx S.A.);
o. NCX 1000 (available from NicOx S.A.);
p. NCX 1020 (available from NicOx S.A.);

q. AZD 4717 (available from NicOx S.A.);

r. NCX 1510/NCX 1512 (available from NicOx S.A.);

s. NCX 2216 (available from NicOx S.A.);

t. NCX 4040 (available from NicOx S.A.);

u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;

v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;

w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;

x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;

y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;

z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;

aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;

bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;

cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;

dd. Nitric oxide donors as disclosed in U.S. Patent No.5,714,511;

ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911; and

ff. Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

The identification of further compounds that have nitric oxide donor activity and would therefore be useful in the present invention can be determined by release profile and/or induced vasospasm studies as described in US Patent Nos. 6,451,337 and 6,358,536, as well as Moon (2002) *IBJU Int.* 89: 942-9 and Fathian-Sabet *et al.* (2001) *J. Urol.* 165: 1724-9.

Enantiomers and Diasteromers

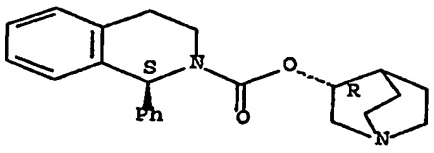
Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes D and L, or (+) or (-), designate the sign of rotation of plane-polarized light by the compound, with L or (-) meaning that the compound is levorotatory. In contrast, a compound prefixed with D or (+) is dextrorotatory. There is no correlation between nomenclature for the absolute stereochemistry and for the rotation

of an enantiomer. Thus, D-lactic acid is the same as (-)-lactic acid, and L-lactic acid is the same as (+)-lactic acid. For a given chemical structure, each of a pair of enantiomers are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric, or racemic, mixture.

Stereochemical purity is important in the pharmaceutical field, where many of the most often prescribed drugs exhibit chirality. For example, the L-enantiomer of the beta-adrenergic blocking agent, propranolol, is known to be 100 times more potent than its D-enantiomer. Additionally, optical purity is important in the pharmaceutical drug field because certain isomers have been found to impart a deleterious effect, rather than an advantageous or inert effect. For example, it is believed that the D-enantiomer of thalidomide is a safe and effective sedative when prescribed for the control of morning sickness during pregnancy, whereas its corresponding L-enantiomer is believed to be a potent teratogen.

When two chiral centers exist in one molecule, there are four possible stereoisomers: (R,R), (S,S), (R,S), and (S,R). Of these, (R,R) and (S,S) are an example of a pair of enantiomers (mirror images of each other), which typically share chemical properties and melting points just like any other enantiomeric pair. The mirror images of (R,R) and (S,S) are not, however, superimposable on (R,S) and (S,R). This relationship is called diastereoisomeric, and the (S,S) molecule is a diastereoisomer of the (R,S) molecule, whereas the (R,R) molecule is a diastereoisomer of the (S,R) molecule.

An example of a compound with two chiral centers is the antimuscarinic solifenacin. Solifenacin is described in U.S. Patent No. 6,174,896 and is represented by the following chemical formula:



Because solifenacin has two chiral centers, diastereomers as well as enantiomers exist for this molecule (see U.S. Patent No. 6,174,896). Solifenacin succinate (development number YM-905) is a salt form of solifenacin that is co-promoted as Vesicare® by

Yamanouchi Pharmaceutical Co., Ltd. (through Yamanouchi Pharma America) and GlaxoSmithKline as an investigational muscarinic antagonist that is thought to act on receptors in the smooth muscle of the bladder. Solifenacin was discovered and developed by Yamanouchi, and a New Drug Application was submitted to the U.S. Food and Drug Administration by YPA in December 2002 for solifenacin succinate. A market authorization application for Vesicare® was submitted in Europe in January 2003, and Yamanouchi has initiated Phase III clinical trials for Vesicare® in Japan. Other salt forms of solifenacin have also been specifically described by Yamanouchi, including solifenacine monohydrochloride (development number YM-53705).

For use in the present invention, any diastereomer or enantiomer of an active agent as disclosed herein, can be administered to treat painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients.

Formulations

Formulations of the present invention may include, but are not limited to, continuous, as needed, short-term, rapid-offset, controlled release, sustained release, delayed release, and pulsatile release formulations.

Compositions of the invention comprise $\alpha_2\delta$ subunit calcium channel modulators in combination with one or more compounds with smooth muscle modulatory effects, including antimuscarinics (particularly those that do not have an amine embedded in an 8-azabicyclo[3.2.1]octan-3-ol skeleton), β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors. The compositions are administered in therapeutically effective amounts to a patient in need thereof for treating painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. It is recognized that the compositions may be administered by any means of administration as long as an effective amount for the treatment of painful and non-painful symptoms associated with lower urinary tract disorders in normal and spinal cord injured patients is delivered.

Any of the active agents may be administered in the form of a salt, ester, amide, prodrug, active metabolite, derivative, or the like, provided that the salt, ester, amide, prodrug or derivative is suitable pharmacologically, i.e., effective in the present method.

Salts, esters, amides, prodrugs and other derivatives of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 4th Ed. (New York: Wiley-Interscience, 1992). For example, acid addition salts are prepared from the free base using conventional methodology, and involves reaction with a suitable acid. Suitable acids for preparing acid addition salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Particularly preferred acid addition salts of the active agents herein are salts prepared with organic acids. Conversely, preparation of basic salts of acid moieties which may be present on an active agent are prepared in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like.

Preparation of esters involves functionalization of hydroxyl and/or carboxyl groups that may be present within the molecular structure of the drug. The esters are typically acyl-substituted derivatives of free alcohol groups, i.e., moieties that are derived from carboxylic acids of the formula RCOOH where R is alkyl, and preferably is lower alkyl. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Amides and prodrugs may also be prepared using techniques known to those skilled in the art or described in the pertinent literature. For example, amides may be prepared from esters, using suitable amine reactants, or they may be prepared from an anhydride or an acid chloride by reaction with ammonia or a lower alkyl amine. Prodrugs are typically prepared by covalent attachment of a moiety, which results in a compound that is therapeutically inactive until modified by an individual's metabolic system.

One set of formulations for gabapentin are those marketed by Pfizer Inc. under the brand name Neurontin®. Neurontin® Capsules, Neurontin® Tablets, and Neurontin®

Oral Solution are supplied either as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, elliptical film-coated tablets containing 600 mg and 800 mg of gabapentin or an oral solution containing 250 mg/5 mL of gabapentin. The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100 mg capsule shell contains gelatin and titanium dioxide. The 300 mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400 mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The inactive ingredients for the tablets are poloxamer 407, copolyvidonum, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax and purified water. The inactive ingredients for the oral solution are glycerin, xylitol, purified water and artificial cool strawberry anise flavor. In addition to these formulations, gabapentin and formulations are generally described in the following patents: US 6,645,528; US 6,627,211; US 6,569,463; US 6,544,998; US 6,531,509; 6,495,669; US 6,465,012; US 6,346,270; US 6,294,198; US 6,294,192; US 6,207,685; US 6,127,418; US 6,024,977; US 6,020,370; US 5,906,832; US 5,876,750; and US 4,960,931.

Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature. In addition, chiral active agents may be in isomerically pure form, or they may be administered as a racemic mixture of isomers.

Pharmaceutical Compositions and Dosage Forms

Suitable compositions and dosage forms include tablets, capsules, caplets, pills, gel caps, troches, dispersions, suspensions, solutions, syrups, transdermal patches, gels, powders, magmas, lozenges, creams, pastes, plasters, lotions, discs, suppositories, liquid sprays for nasal or oral administration, dry powder or aerosolized formulations for inhalation, compositions and formulations for intravesical administration and the like. Further, those of ordinary skill in the art can readily deduce that suitable formulations involving these compositions and dosage forms, including those formulations as described elsewhere herein.

Oral Dosage Forms

Oral dosage forms include tablets, capsules, caplets, solutions, suspensions and/or syrups, and may also comprise a plurality of granules, beads, powders or pellets that may or may not be encapsulated. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts, e.g., in Remington: The Science and Practice of Pharmacy, supra). Tablets and capsules represent the most convenient oral dosage forms, in which case solid pharmaceutical carriers are employed.

Tablets may be manufactured using standard tablet processing procedures and equipment. One method for forming tablets is by direct compression of a powdered, crystalline or granular composition containing the active agent(s), alone or in combination with one or more carriers, additives, or the like. As an alternative to direct compression, tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist or otherwise tractable material; however, compression and granulation techniques are preferred.

In addition to the active agent(s), then, tablets prepared for oral administration using the method of the invention will generally contain other materials such as binders, diluents, lubricants, disintegrants, fillers, stabilizers, surfactants, preservatives, coloring agents, flavoring agents and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, propylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Diluents are typically necessary to increase bulk so that a practical size tablet is ultimately provided. Suitable diluents include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma, glycerin, magnesium stearate, calcium stearate, and stearic acid. Stearates, if present, preferably represent at

no more than approximately 2 wt. % of the drug-containing core. Disintegrants are used to facilitate disintegration of the tablet, and are generally starches, clays, celluloses, algins, gums or crosslinked polymers. Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride and sorbitol. Stabilizers are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions. Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents.

The dosage form may also be a capsule, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. (See, for e.g., Remington: The Science and Practice of Pharmacy, supra), which describes materials and methods for preparing encapsulated pharmaceuticals. If the active agent-containing composition is present within the capsule in liquid form, a liquid carrier is necessary to dissolve the active agent(s). The carrier must be compatible with the capsule material and all components of the pharmaceutical composition, and must be suitable for ingestion.

Solid dosage forms, whether tablets, capsules, caplets, or particulates, may, if desired, be coated so as to provide for delayed release. Dosage forms with delayed release coatings may be manufactured using standard coating procedures and equipment. Such procedures are known to those skilled in the art and described in the pertinent texts (See, for e.g., Remington: The Science and Practice of Pharmacy, supra). Generally, after preparation of the solid dosage form, a delayed release coating composition is applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. Delayed release coating compositions comprise a polymeric material, e.g., cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose proprionate phthalate, polyvinyl acetate phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethylcellulose,

hydroxypropyl methylcellulose acetate succinate, polymers and copolymers formed from acrylic acid, methacrylic acid, and/or esters thereof.

Sustained release dosage forms provide for drug release over an extended time period, and may or may not be delayed release. Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms are formulated by dispersing a drug within a matrix of a gradually bioerodible (hydrolyzable) material such as an insoluble plastic, a hydrophilic polymer, or a fatty compound, or by coating a solid, drug-containing dosage form with such a material. Insoluble plastic matrices may be comprised of, for example, polyvinyl chloride or polyethylene. Hydrophilic polymers useful for providing a sustained release coating or matrix cellulosic polymers include, without limitation: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, hydroxypropylcellulose phthalate, cellulose hexahydrophthalate, cellulose acetate hexahydrophthalate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, with a terpolymer of ethyl acrylate, methyl methacrylate and trimethylammonioethyl methacrylate chloride (sold under the tradename Eudragit RS) preferred; vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, and shellac n-butyl stearate. Fatty compounds for use as a sustained release matrix material include, but are not limited to, waxes generally (e.g., carnauba wax) and glyceryl tristearate.

Transmucosal Compositions and Dosage Forms

Although the present compositions may be administered orally, other modes of administration are suitable as well. For example, transmucosal administration may be advantageously employed. Transmucosal administration is carried out using any type of formulation or dosage unit suitable for application to mucosal tissue. For example, the

selected active agent may be administered to the buccal mucosa in an adhesive tablet or patch, sublingually administered by placing a solid dosage form under the tongue, lingually administered by placing a solid dosage form on the tongue, administered nasally as droplets or a nasal spray, administered by inhalation of an aerosol formulation, a non-aerosol liquid formulation, or a dry powder, placed within or near the rectum ("transrectal" formulations), or administered to the urethra as a suppository, ointment, or the like.

Preferred buccal dosage forms will typically comprise a therapeutically effective amount of an active agent and a bioerodible (hydrolyzable) polymeric carrier that may also serve to adhere the dosage form to the buccal mucosa. The buccal dosage unit is fabricated so as to erode over a predetermined time period, wherein drug delivery is provided essentially throughout. The time period is typically in the range of from about 1 hour to about 72 hours. Preferred buccal delivery preferably occurs over a time period of from about 2 hours to about 24 hours. Buccal drug delivery for short term use should preferably occur over a time period of from about 2 hours to about 8 hours, more preferably over a time period of from about 3 hours to about 4 hours. As needed buccal drug delivery preferably will occur over a time period of from about 1 hour to about 12 hours, more preferably from about 2 hours to about 8 hours, most preferably from about 3 hours to about 6 hours. Sustained buccal drug delivery will preferably occur over a time period of from about 6 hours to about 72 hours, more preferably from about 12 hours to about 48 hours, most preferably from about 24 hours to about 48 hours. Buccal drug delivery, as will be appreciated by those skilled in the art, avoids the disadvantages encountered with oral drug administration, e.g., slow absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver.

The "therapeutically effective amount" of the active agent in the buccal dosage unit will of course depend on the potency of the agent and the intended dosage, which, in turn, is dependent on the particular individual undergoing treatment, the specific indication, and the like. The buccal dosage unit will generally contain from about 1.0 wt. % to about 60 wt. % active agent, preferably on the order of from about 1 wt. % to about 30 wt. % active agent. With regard to the bioerodible (hydrolyzable) polymeric carrier, it

will be appreciated that virtually any such carrier can be used, so long as the desired drug release profile is not compromised, and the carrier is compatible with the active agents to be administered and any other components of the buccal dosage unit. Generally, the polymeric carrier comprises a hydrophilic (water-soluble and water-swellable) polymer that adheres to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B. F. Goodrich, is one such polymer). Other suitable polymers include, but are not limited to: hydrolyzed polyvinylalcohol; polyethylene oxides (e.g., Sentry Polyox® water soluble resins, available from Union Carbide); polyacrylates (e.g., Gantrez®, which may be obtained from GAF); vinyl polymers and copolymers; polyvinylpyrrolidone; dextran; guar gum; pectins; starches; and cellulosic polymers such as hydroxypropyl methylcellulose, (e.g., Methocel®, which may be obtained from the Dow Chemical Company), hydroxypropyl cellulose (e.g., Klucel®, which may also be obtained from Dow), hydroxypropyl cellulose ethers (see, e.g., U.S. Pat. No. 4,704,285 to Alderman), hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, and the like.

Other components may also be incorporated into the buccal dosage forms described herein. The additional components include, but are not limited to, disintegrants, diluents, binders, lubricants, flavoring, colorants, preservatives, and the like. Examples of disintegrants that may be used include, but are not limited to, cross-linked polyvinylpyrrolidones, such as crospovidone (e.g., Polyplasdone® XL, which may be obtained from GAF), cross-linked carboxylic methylcelluloses, such as croscarmelose (e.g., Ac-di-sol®, which may be obtained from FMC), alginic acid, and sodium carboxymethyl starches (e.g., Explotab®, which may be obtained from Edward Medell Co., Inc.), methylcellulose, agar bentonite and alginic acid. Suitable diluents are those which are generally useful in pharmaceutical formulations prepared using compression techniques, e.g., dicalcium phosphate dihydrate (e.g., Di-Tab®, which may be obtained from Stauffer), sugars that have been processed by cocrystallization with dextrin (e.g., co-crystallized sucrose and dextrin such as Di-Pak®, which may be obtained from Amstar), calcium phosphate, cellulose, kaolin, mannitol, sodium chloride, dry starch,

powdered sugar and the like. Binders, if used, are those that enhance adhesion. Examples of such binders include, but are not limited to, starch, gelatin and sugars such as sucrose, dextrose, molasses, and lactose. Particularly preferred lubricants are stearates and stearic acid, and an optimal lubricant is magnesium stearate.

Sublingual and lingual dosage forms include tablets, creams, ointments, lozenges, pastes, and any other solid dosage form where the active ingredient is admixed into a disintegrable matrix. The tablet, cream, ointment or paste for sublingual or lingual delivery comprises a therapeutically effective amount of the selected active agent and one or more conventional nontoxic carriers suitable for sublingual or lingual drug administration. The sublingual and lingual dosage forms of the present invention can be manufactured using conventional processes. The sublingual and lingual dosage units are fabricated to disintegrate rapidly. The time period for complete disintegration of the dosage unit is typically in the range of from about 10 seconds to about 30 minutes, and optimally is less than 5 minutes.

Other components may also be incorporated into the sublingual and lingual dosage forms described herein. The additional components include, but are not limited to binders, disintegrants, wetting agents, lubricants, and the like. Examples of binders that may be used include water, ethanol, polyvinylpyrrolidone; starch solution gelatin solution, and the like. Suitable disintegrants include dry starch, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic monoglyceride, lactose, and the like. Wetting agents, if used, include glycerin, starches, and the like. Particularly preferred lubricants are stearates and polyethylene glycol. Additional components that may be incorporated into sublingual and lingual dosage forms are known, or will be apparent, to those skilled in this art (See, e.g., Remington: The Science and Practice of Pharmacy, supra).

For transurethral administration, the formulation comprises a urethral dosage form containing the active agent and one or more selected carriers or excipients, such as water, silicone, waxes, petroleum jelly, polyethylene glycol ("PEG"), propylene glycol ("PG"), liposomes, sugars such as mannitol and lactose, and/or a variety of other materials, with polyethylene glycol and derivatives thereof particularly preferred.

Depending on the particular active agent administered, it may be desirable to incorporate a transurethral permeation enhancer in the urethral dosage form. Examples of suitable transurethral permeation enhancers include dimethylsulfoxide ("DMSO"), dimethyl formamide ("DMF"), N, N-dimethylacetamide ("DMA"), decylmethylsulfoxide ("C_{10} MSO"), polyethylene glycol monolaurate ("PEGML"), glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone® from Nelson Research & Development Co., Irvine, Calif.), SEPA® (available from Macrochem Co., Lexington, Mass.), surfactants as discussed above, including, for example, Tergitol®, Nonoxynol-9® and TWEEN-80®, and lower alkanols such as ethanol.

Transurethral drug administration, as explained in U.S. Pat. Nos. 5,242,391, 5,474,535, 5,686,093 and 5,773,020, can be carried out in a number of different ways using a variety of urethral dosage forms. For example, the drug can be introduced into the urethra from a flexible tube, squeeze bottle, pump or aerosol spray. The drug may also be contained in coatings, pellets or suppositories that are absorbed, melted or bioeroded in the urethra. In certain embodiments, the drug is included in a coating on the exterior surface of a penile insert. It is preferred, although not essential, that the drug be delivered from at least about 3 cm into the urethra, and preferably from at least about 7 cm into the urethra. Generally, delivery from at least about 3 cm to about 8 cm into the urethra will provide effective results in conjunction with the present method.

Urethral suppository formulations containing PEG or a PEG derivative may be conveniently formulated using conventional techniques, e.g., compression molding, heat molding or the like, as will be appreciated by those skilled in the art and as described in the pertinent literature and pharmaceutical texts. (See, e.g., Remington: The Science and Practice of Pharmacy, supra), which discloses typical methods of preparing pharmaceutical compositions in the form of urethral suppositories. The PEG or PEG derivative preferably has a molecular weight in the range of from about 200 to about 2,500 g/mol, more preferably in the range of from about 1,000 to about 2,000 g/mol. Suitable polyethylene glycol derivatives include polyethylene glycol fatty acid esters, for example, polyethylene glycol monostearate, polyethylene glycol sorbitan esters, e.g., polysorbates, and the like. Depending on the particular active agent, it may also be

preferred that urethral suppositories contain one or more solubilizing agents effective to increase the solubility of the active agent in the PEG or other transurethral vehicle.

It may be desirable to deliver the active agent in a urethral dosage form that provides for controlled or sustained release of the agent. In such a case, the dosage form comprises a biocompatible, biodegradable material, typically a biodegradable polymer. Examples of such polymers include polyesters, polyalkylcyanoacrylates, polyorthoesters, polyanhydrides, albumin, gelatin and starch. As explained, for example, in PCT Publication No. WO 96/40054, these and other polymers can be used to provide biodegradable microparticles that enable controlled and sustained drug release, in turn minimizing the required dosing frequency.

The urethral dosage form will preferably comprise a suppository that is on the order of from about 2 to about 20 mm in length, preferably from about 5 to about 10 mm in length, and less than about 5 mm in width, preferably less than about 2 mm in width. The weight of the suppository will typically be in the range of from about 1 mg to about 100 mg, preferably in the range of from about 1 mg to about 50 mg. However, it will be appreciated by those skilled in the art that the size of the suppository can and will vary, depending on the potency of the drug, the nature of the formulation, and other factors.

Transurethral drug delivery may involve an "active" delivery mechanism such as iontophoresis, electroporation or phonophoresis. Devices and methods for delivering drugs in this way are well known in the art. Iontophoretically assisted drug delivery is, for example, described in PCT Publication No. WO 96/40054, cited above. Briefly, the active agent is driven through the urethral wall by means of an electric current passed from an external electrode to a second electrode contained within or affixed to a urethral probe.

Preferred transrectal dosage forms include rectal suppositories, creams, ointments, and liquid formulations (enemas). The suppository, cream, ointment or liquid formulation for transrectal delivery comprises a therapeutically effective amount of the selected phosphodiesterase inhibitor and one or more conventional nontoxic carriers suitable for transrectal drug administration. The transrectal dosage forms of the present invention can be manufactured using conventional processes. The transrectal dosage unit can be fabricated to disintegrate rapidly or over a period of several hours. The time period

for complete disintegration is preferably in the range of from about 10 minutes to about 6 hours, and optimally is less than about 3 hours.

Other components may also be incorporated into the transrectal dosage forms described herein. The additional components include, but are not limited to, stiffening agents, antioxidants, preservatives, and the like. Examples of stiffening agents that may be used include, for example, paraffin, white wax and yellow wax. Preferred antioxidants, if used, include sodium bisulfite and sodium metabisulfite.

Preferred vaginal or perivaginal dosage forms include vaginal suppositories, creams, ointments, liquid formulations, pessaries, tampons, gels, pastes, foams or sprays. The suppository, cream, ointment, liquid formulation, pessary, tampon, gel, paste, foam or spray for vaginal or perivaginal delivery comprises a therapeutically effective amount of the selected active agent and one or more conventional nontoxic carriers suitable for vaginal or perivaginal drug administration. The vaginal or perivaginal forms of the present invention can be manufactured using conventional processes as disclosed in Remington: The Science and Practice of Pharmacy, supra (see also drug formulations as adapted in U.S. Patent Nos. 6,515,198; 6,500,822; 6,417,186; 6,416,779; 6,376,500; 6,355,641; 6,258,819; 6,172,062; and 6,086,909). The vaginal or perivaginal dosage unit can be fabricated to disintegrate rapidly or over a period of several hours. The time period for complete disintegration is preferably in the range of from about 10 minutes to about 6 hours, and optimally is less than about 3 hours.

Other components may also be incorporated into the vaginal or perivaginal dosage forms described herein. The additional components include, but are not limited to, stiffening agents, antioxidants, preservatives, and the like. Examples of stiffening agents that may be used include, for example, paraffin, white wax and yellow wax. Preferred antioxidants, if used, include sodium bisulfite and sodium metabisulfite.

The active agents may also be administered intranasally or by inhalation. Compositions for intranasal administration are generally liquid formulations for administration as a spray or in the form of drops, although powder formulations for intranasal administration, e.g., insufflations, are also known, as are nasal gels, creams, pastes or ointments. For liquid formulations, the active agent can be formulated into a solution, e.g., water or isotonic saline, buffered or unbuffered, or as a suspension.

Preferably, such solutions or suspensions are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or, from about pH 6.0 to about pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. Furthermore, various devices are available in the art for the generation of drops, droplets and sprays, including droppers, squeeze bottles, and manually and electrically powered intranasal pump dispensers. Active agent containing intranasal carriers may also include nasal gels, creams, pastes or ointments with a viscosity of, e.g., from about 10 to about 6500 cps, or greater, depending on the desired sustained contact with the nasal mucosal surfaces. Such carrier viscous formulations may be based upon, simply by way of example, alkylcelluloses and/or other biocompatible carriers of high viscosity well known to the art (see e.g., Remington: The Science and Practice of Pharmacy, supra). Other ingredients, such as art known preservatives, colorants, lubricating or viscous mineral or vegetable oils, perfumes, natural or synthetic plant extracts such as aromatic oils, and humectants and viscosity enhancers such as, e.g., glycerol, can also be included to provide additional viscosity, moisture retention and a pleasant texture and odor for the formulation. Formulations for inhalation may be prepared as an aerosol, either a solution aerosol in which the active agent is solubilized in a carrier (e.g., propellant) or a dispersion aerosol in which the active agent is suspended or dispersed throughout a carrier and an optional solvent. Non-aerosol formulations for inhalation may take the form of a liquid, typically an aqueous suspension, although aqueous solutions may be used as well. In such a case, the carrier is typically a sodium chloride solution having a concentration such that the formulation is isotonic relative to normal body fluid. In addition to the carrier, the liquid formulations may contain water and/or excipients including an antimicrobial preservative (e.g., benzalkonium chloride, benzethonium chloride, chlorobutanol, phenylethyl alcohol, thimerosal and combinations thereof), a buffering agent (e.g., citric acid, potassium metaphosphate, potassium phosphate, sodium acetate, sodium citrate, and combinations thereof), a surfactant (e.g., polysorbate 80, sodium lauryl sulfate, sorbitan monopalmitate and combinations thereof), and/or a suspending agent (e.g., agar, bentonite, microcrystalline cellulose, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, tragacanth, veegum and combinations thereof). Non-aerosol

formulations for inhalation may also comprise dry powder formulations, particularly insufflations in which the powder has an average particle size of from about 0.1 μm to about 50 μm, preferably from about 1 μm to about 25 μm.

Topical Formulations

Topical formulations may be in any form suitable for application to the body surface, and may comprise, for example, an ointment, cream, gel, lotion, solution, paste or the like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres. Preferred topical formulations herein are ointments, creams and gels.

Ointments, as is well known in the art of pharmaceutical formulation, are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and, preferably, will provide for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing. As explained in Remington: The Science and Practice of Pharmacy, supra, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight (See, e.g., Remington: The Science and Practice of Pharmacy, supra).

Creams, as also well known in the art, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in

volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant.

As will be appreciated by those working in the field of pharmaceutical formulation, gels-are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the carrier liquid, which is typically aqueous, but also, preferably, contain an alcohol and, optionally, an oil. Preferred "organic macromolecules," i.e., gelling agents, are crosslinked acrylic acid polymers such as the "carbomer" family of polymers, e.g., carboxypolyalkylenes that may be obtained commercially under the Carbopol® trademark. Also preferred are hydrophilic polymers such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers and polyvinylalcohol; cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

Various additives, known to those skilled in the art, may be included in the topical formulations. For example, solubilizers may be used to solubilize certain active agents. For those drugs having an unusually low rate of permeation through the skin or mucosal tissue, it may be desirable to include a permeation enhancer in the formulation; suitable enhancers are as described elsewhere herein.

Transdermal Administration

The compounds of the invention may also be administered through the skin or mucosal tissue using conventional transdermal drug delivery systems, wherein the agent is contained within a laminated structure (typically referred to as a transdermal "patch") that serves as a drug delivery device to be affixed to the skin. Transdermal drug delivery may involve passive diffusion or it may be facilitated using electrotransport, e.g., iontophoresis. In a typical transdermal "patch," the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one type of patch,

referred to as a "monolithic" system, the reservoir is comprised of a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. Alternatively, the drug-containing reservoir and skin contact adhesive are separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form.

The backing layer in these laminates, which serves as the upper surface of the device, functions as the primary structural element of the laminated structure and provides the device with much of its flexibility. The material selected for the backing material should be selected so that it is substantially impermeable to the active agent and any other materials that are present, the backing is preferably made of a sheet or film of a flexible elastomeric material. Examples of polymers that are suitable for the backing layer include polyethylene, polypropylene, polyesters, and the like.

During storage and prior to use, the laminated structure includes a release liner. Immediately prior to use, this layer is removed from the device to expose the basal surface thereof, either the drug reservoir or a separate contact adhesive layer, so that the system may be affixed to the skin. The release liner should be made from a drug/vehicle impermeable material.

Transdermal drug delivery systems may in addition contain a skin permeation enhancer. That is, because the inherent permeability of the skin to some drugs may be too low to allow therapeutic levels of the drug to pass through a reasonably sized area of unbroken skin, it is necessary to coadminister a skin permeation enhancer with such drugs. Suitable enhancers are well known in the art and include, for example, those enhancers listed above in transmucosal compositions.

Parenteral Administration

Parenteral administration, if used, is generally characterized by injection, including intramuscular, intraperitoneal, intravenous (IV) and subcutaneous injection. Injectable formulations can be prepared in conventional forms, either as liquid solutions

or suspensions; solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Preferably, sterile injectable suspensions are formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable formulation may also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. A more recently revised approach for parenteral administration involves use of a slow release or sustained release system (See, e.g., U.S. Pat. No. 3,710,795).

Intravesical Administration

Intravesical administration, if used, is generally characterized by administration directly into the bladder and may include methods as described elsewhere herein. Other methods of intravesical administration may include those described in U.S. Patent Nos. 6,207,180 and 6,039,967, as well as other methods that are known to one of skill in the art.

Intrathecal Administration

Intrathecal administration, if used, is generally characterized by administration directly into the intrathecal space (where fluid flows around the spinal cord).

One common system utilized for intrathecal administration is the APT Intrathecal treatment system available from Medtronic, Inc. APT Intrathecal uses a small pump that is surgically placed under the skin of the abdomen to deliver medication directly into the intrathecal space. The medication is delivered through a small tube called a catheter that is also surgically placed. The medication can then be administered directly to cells in the spinal cord involved in conveying sensory and motor signals associated with lower urinary tract disorders.

Another system available from Medtronic that is commonly utilized for intrathecal administration is the is the fully implantable, programmable SynchroMed® Infusion System. The SynchroMed® Infusion System has two parts that are both placed

in the body during a surgical procedure: the catheter and the pump. The catheter is a small, soft tube. One end is connected to the catheter port of the pump, and the other end is placed in the intrathecal space. The pump is a round metal device about one inch (2.5 cm) thick, three inches (8.5 cm) in diameter, and weighs about six ounces (205 g) that stores and releases prescribed amounts of medication directly into the intrathecal space. It is made of titanium, a lightweight, medical-grade metal. The reservoir is the space inside the pump that holds the medication. The fill port is a raised center portion of the pump through which the pump is refilled. The doctor or a nurse inserts a needle through the patient's skin and through the fill port to fill the pump. Some pumps have a side catheter access port that allows the doctor to inject other medications or sterile solutions directly into the catheter, bypassing the pump.

The SynchroMed® pump automatically delivers a controlled amount of medication through the catheter to the intrathecal space around the spinal cord, where it is most effective. The exact dosage, rate and timing prescribed by the doctor are entered in the pump using a programmer, an external computer-like device that controls the pump's memory. Information about the patient's prescription is stored in the pump's memory. The doctor can easily review this information by using the programmer. The programmer communicates with the pump by radio signals that allow the doctor to tell how the pump is operating at any given time. The doctor also can use the programmer to change your medication dosage.

Methods of intrathecal administration may include those described above available from Medtronic, as well as other methods that are known to one of skill in the art.

Additional Dosage Formulations and Drug Delivery Systems

As compared with traditional drug delivery approaches, some controlled release technologies rely upon the modification of both macromolecules and synthetic small molecules to allow them to be actively instead of passively absorbed into the body. For example, XenoPort Inc. utilizes technology that takes existing molecules and re-engineers them to create new chemical entities (unique molecules) that have improved pharmacologic properties to either: 1) lengthen the short half-life of a drug; 2) overcome

poor absorption; and/or 3) deal with poor drug distribution to target tissues. Techniques to lengthen the short half-life of a drug include the use of prodrugs with slow cleavage rates to release drugs over time or that engage transporters in small and large intestines to allow the use of oral sustained delivery systems, as well as drugs that engage active transport systems. Examples of such controlled release formulations, tablets, dosage forms, and drug delivery systems, and that are suitable for use with the present invention, are described in the following published US and PCT patent applications assigned to Xenoport Inc.: US20030158254; US20030158089; US20030017964; US2003130246; WO02100172; WO02100392; WO02100347; WO02100344; WO0242414; WO0228881; WO0228882; WO0244324; WO0232376; WO0228883; and WO0228411. Some other controlled release technologies rely upon methods that promote or enhance gastric retention, such as those developed by Depomed Inc. Because many drugs are best absorbed in the stomach and upper portions of the small intestine, Depomed has developed tablets that swell in the stomach during the postprandial or fed mode so that they are treated like undigested food. These tablets therefore sit safely and neutrally in the stomach for 6, 8, or more hours and deliver drug at a desired rate and time to upper gastrointestinal sites. Specific technologies in this area include: 1) tablets that slowly erode in gastric fluids to deliver drugs at almost a constant rate (particularly useful for highly insoluble drugs); 2) bi-layer tablets that combine drugs with different characteristics into a single table (such as a highly insoluble drug in an erosion layer and a soluble drug in a diffusion layer for sustained release of both); and 3) combination tablets that can either deliver drugs simultaneously or in sequence over a desired period of time (including an initial burst of a fast acting drug followed by slow and sustained delivery of another drug). Examples of such controlled release formulations that are suitable for use with the present invention and that rely upon gastric retention during the postprandial or fed mode, include tablets, dosage forms, and drug delivery systems in the following US patents assigned to Depomed Inc.: US 6,488,962; US 6,451,808; US 6,340,475; US 5,972,389; US 5,582,837; and US 5,007,790. Examples of such controlled release formulations that are suitable for use with the present invention and that rely upon gastric retention during the postprandial or fed mode, include tablets, dosage forms, and drug delivery systems in the following published US and PCT patent

applications assigned to Depomed Inc.: US20030147952; US20030104062; US20030104053; US20030104052; US20030091630; US20030044466; US20030039688; US20020051820; WO0335040; WO0335039; WO0156544; WO0132217; WO9855107; WO9747285; and WO9318755.

Other controlled release systems include those developed by ALZA Corporation based upon: 1) osmotic technology for oral delivery; 2) transdermal delivery via patches; 3) liposomal delivery via intravenous injection; 4) osmotic technology for long-term delivery via implants; and 5) depot technology designed to deliver agents for periods of days to a month. ALZA oral delivery systems include those that employ osmosis to provide precise, controlled drug delivery for up to 24 hours for both poorly soluble and highly soluble drugs, as well as those that deliver high drug doses meeting high drug loading requirements. ALZA controlled transdermal delivery systems provide drug delivery through intact skin for as long as one week with a single application to improve drug absorption and deliver constant amounts of drug into the bloodstream over time. ALZA liposomal delivery systems involve lipid nanoparticles that evade recognition by the immune system because of their unique polyethylene glycol (PEG) coating, allowing the precise delivery of drugs to disease-specific areas of the body. ALZA also has developed osmotically driven systems to enable the continuous delivery of small drugs, peptides, proteins, DNA and other bioactive macromolecules for up to one year for systemic or tissue-specific therapy. Finally, ALZA depot injection therapy is designed to deliver biopharmaceutical agents and small molecules for periods of days to a month using a nonaqueous polymer solution for the stabilization of macromolecules and a unique delivery profile.

Examples of controlled release formulations, tablets, dosage forms, and drug delivery systems that are suitable for use with the present invention are described in the following US patents assigned to ALZA Corporation: US 4,367,741; US 4,402,695; US 4,418,038; US 4,434,153; US 4,439,199; US 4,450,198; US 4,455,142; US 4,455,144; US 4,484,923; US 4,486,193; US 4,489,197; US 4,511,353; US 4,519,801; US 4,526,578; US 4,526,933; US 4,534,757; US 4,553,973; US 4,559,222; US 4,564,364; US 4,578,075; US 4,588,580; US 4,610,686; US 4,618,487; US 4,627,851; US 4,629,449; US 4,642,233; US 4,649,043; US 4,650,484; US 4,659,558; US 4,661,105;

US 4,662,880; US 4,675,174; US 4,681,583; US 4,684,524; US 4,692,336; US 4,693,895; US 4,704,119; US 4,705,515; US 4,717,566; US 4,721,613; US 4,723,957; US 4,725,272; US 4,728,498; US 4,743,248; US 4,747,847; US 4,751,071; US 4,753,802; US 4,755,180; US 4,756,314; US 4,764,380; US 4,773,907; US 4,777,049; US 4,781,924; US 4,786,503; US 4,788,062; US 4,810,502; US 4,812,313; US 4,816,258; US 4,824,675; US 4,834,979; US 4,837,027; US 4,842,867; US 4,846,826; US 4,847,093; US 4,849,226; US 4,851,229; US 4,851,231; US 4,851,232; US 4,853,229; US 4,857,330; US 4,859,470; US 4,863,456; US 4,863,744; US 4,865,598; US 4,867,969; US 4,871,548; US 4,872,873; US 4,874,388; US 4,876,093; US 4,892,778; US 4,902,514; US 4,904,474; US 4,913,903; US 4,915,949; US 4,915,952; US 4,917,895; US 4,931,285; US 4,946,685; US 4,948,592; US 4,954,344; US 4,957,494; US 4,960,416; US 4,961,931; US 4,961,932; US 4,963,141; US 4,966,769; US 4,971,790; US 4,976,966; US 4,986,987; US 5,006,346; US 5,017,381; US 5,019,397; US 5,023,076; US 5,023,088; US 5,024,842; US 5,028,434; US 5,030,454; US 5,071,656; US 5,077,054; US 5,082,668; US 5,104,390; US 5,110,597; US 5,122,128; US 5,125,894; US 5,141,750; US 5,141,752; US 5,156,850; US 5,160,743; US 5,160,744; US 5,169,382; US 5,171,576; US 5,176,665; US 5,185,158; US 5,190,765; US 5,198,223; US 5,198,229; US 5,200,195; US 5,200,196; US 5,204,116; US 5,208,037; US 5,209,746; US 5,221,254; US 5,221,278; US 5,229,133; US 5,232,438; US 5,232,705; US 5,236,689; US 5,236,714; US 5,240,713; US 5,246,710; US 5,246,711; US 5,252,338; US 5,254,349; US 5,266,332; US 5,273,752; US 5,284,660; US 5,286,491; US 5,308,348; US 5,318,558; US 5,320,850; US 5,322,502; US 5,326,571; US 5,330,762; US 5,338,550; US 5,340,590; US 5,342,623; US 5,344,656; US 5,348,746; US 5,358,721; US 5,364,630; US 5,376,377; US 5,391,381; US 5,402,777; US 5,403,275; US 5,411,740; US 5,417,675; US 5,417,676; US 5,417,682; US 5,423,739; US 5,424,289; US 5,431,919; US 5,443,442; US 5,443,459; US 5,443,461; US 5,456,679; US 5,460,826; US 5,462,741; US 5,462,745; US 5,489,281; US 5,499,979; US 5,500,222; US 5,512,293; US 5,512,299; US 5,529,787; US 5,531,736; US 5,532,003; US 5,533,971; US 5,534,263; US 5,540,912; US 5,543,156; US 5,571,525; US 5,573,503; US 5,591,124; US 5,593,695; US 5,595,759; US 5,603,954; US 5,607,696; US 5,609,885; US 5,614,211; US 5,614,578; US

5,620,705; US 5,620,708; US 5,622,530; US 5,622,944; US 5,633,011; US 5,639,477; US 5,660,861; US 5,667,804; US 5,667,805; US 5,674,895; US 5,688,518; US 5,698,224; US 5,702,725; US 5,702,727; US 5,707,663; US 5,713,852; US 5,718,700; US 5,736,580; US 5,770,227; US 5,780,058; US 5,783,213; US 5,785,994; US 5,795,591; US 5,811,465; US 5,817,624; US 5,824,340; US 5,830,501; US 5,830,502; US 5,840,754; US 5,858,407; US 5,861,439; US 5,863,558; US 5,876,750; US 5,883,135; US 5,897,878; US 5,904,934; US 5,904,935; US 5,906,832; US 5,912,268; US 5,914,131; US 5,916,582; US 5,932,547; US 5,938,654; US 5,941,844; US 5,955,103; US 5,972,369; US 5,972,370; US 5,972,379; US 5,980,943; US 5,981,489; US 5,983,130; US 5,989,590; US 5,995,869; US 5,997,902; US 6,001,390; US 6,004,309; US 6,004,578; US 6,008,187; US 6,020,000; US 6,034,101; US 6,036,973; US 6,039,977; US 6,057,374; US 6,066,619; US 6,068,850; US 6,077,538; US 6,083,190; US 6,096,339; US 6,106,845; US 6,110,499; US 6,120,798; US 6,120,803; US 6,124,261; US 6,130,200; US 6,146,662; US 6,153,678; US 6,174,547; US 6,183,466; US 6,203,817; US 6,210,712; US 6,210,713; US 6,224,907; US 6,235,712; US 6,245,357; US 6,262,115; US 6,264,990; US 6,267,984; US 6,287,598; US 6,289,241; US 6,331,311; US 6,333,050; US 6,342,249; US 6,346,270; US 6365183; US 6,368,626; US 6,387,403; US 6,419,952; US 6,440,457; US 6,468,961; US 6,491,683; US 6,512,010; US 6,514,530; US 6534089; US 6,544,252; US 6,548,083; US 6,551,613; US 6,572,879; and US 6,596,314.

Other examples of controlled release formulations, tablets, dosage forms, and drug delivery systems that are suitable for use with the present invention are described in the following published US patent application and PCT applications assigned to ALZA Corporation: US20010051183; WO0004886; WO0013663; WO0013674; WO0025753; WO0025790; WO0035419; WO0038650; WO0040218; WO0045790; WO0066126; WO0074650; WO0119337; WO0119352; WO0121211; WO0137815; WO0141742; WO0143721; WO0156543; WO3041684; WO03041685; WO03041757; WO03045352; WO03051341; WO03053400; WO03053401; WO9000416; WO9004965; WO9113613; WO9116884; WO9204011; WO9211843; WO9212692; WO9213521; WO9217239; WO9218102; WO9300071; WO9305843; WO9306819; WO9314813; WO9319739; WO9320127; WO9320134; WO9407562; WO9408572; WO9416699; WO9421262;

WO9427587; WO9427589; WO9503823; WO9519174; WO9529665; WO9600065; WO9613248; WO9625922; WO9637202; WO9640049; WO9640050; WO9640139; WO9640364; WO9640365; WO9703634; WO9800158; WO9802169; WO9814168; WO9816250; WO9817315; WO9827962; WO9827963; WO9843611; WO9907342; WO9912526; WO9912527; WO9918159; WO9929297; WO9929348; WO9932096; WO9932153; WO9948494; WO9956730; WO9958115; and WO9962496.

Andrx Corporation has also developed drug delivery technology suitable for use in the present invention that includes: 1) a pelletized pulsatile delivery system ("PPDS"); 2) a single composition osmotic tablet system ("SCOT"); 3) a solubility modulating hydrogel system ("SMHS"); 4) a delayed pulsatile hydrogel system ("DPHS"); 5) a stabilized pellet delivery system ("SPDS"); 6) a granulated modulating hydrogel system ("GMHS"); 7) a pelletized tablet system ("PELTAB"); 8) a porous tablet system ("PORTAB"); and 9) a stabilized tablet delivery system ("STDS"). PPDS uses pellets that are coated with specific polymers and agents to control the release rate of the microencapsulated drug and is designed for use with drugs that require a pulsed release. SCOT utilizes various osmotic modulating agents as well as polymer coatings to provide a zero-order drug release. SMHS utilizes a hydrogel-based dosage system that avoids the "initial burst effect" commonly observed with other sustained-release hydrogel formulations and that provides for sustained release without the need to use special coatings or structures that add to the cost of manufacturing. DPHS is designed for use with hydrogel matrix products characterized by an initial zero-order drug release followed by a rapid release that is achieved by the blending of selected hydrogel polymers to achieve a delayed pulse. SPDS incorporates a pellet core of drug and protective polymer outer layer, and is designed specifically for unstable drugs, while GMHS incorporates hydrogel and binding polymers with the drug and forms granules that are pressed into tablet form. PELTAB provides controlled release by using a water insoluble polymer to coat discrete drug crystals or pellets to enable them to resist the action of fluids in the gastrointestinal tract, and these coated pellets are then compressed into tablets. PORTAB provides controlled release by incorporating an osmotic core with a continuous polymer coating and a water soluble component that expands the core and creates microporous channels through which drug is released. Finally, STDS includes a

dual layer coating technique that avoids the need to use a coating layer to separate the enteric coating layer from the omeprazole core.

Examples of controlled release formulations, tablets, dosage forms, and drug delivery systems that are suitable for use with the present invention are described in the following US patents assigned to Andrx Corporation: US 5,397,574; US 5,419,917; US 5,458,887; US 5,458,888; US 5,472,708; US 5,508,040; US 5,558,879; US 5,567,441; US 5,654,005; US 5,728,402; US 5,736,159; US 5,830,503; US 5,834,023; US 5,837,379; US 5,916,595; US 5,922,352; US 6,099,859; US 6,099,862; US 6,103,263; US 6,106,862; US 6,156,342; US 6,177,102; US 6,197,347; US 6,210,716; US 6,238,703; US 6,270,805; US 6,284,275; US 6,485,748; US 6,495,162; US 6,524,620; US 6,544,556; US 6,589,553; US 6,602,522; and US 6,610,326.

Examples of controlled release formulations, tablets, dosage forms, and drug delivery systems that are suitable for use with the present invention are described in the following published US and PCT patent applications assigned to Andrx Corporation: US20010024659; US20020115718; US20020156066; WO0004883; WO0009091; WO0012097; WO0027370; WO0050010; WO0132161; WO0134123; WO0236077; WO0236100; WO02062299; WO02062824; WO02065991; WO02069888; WO02074285; WO03000177; WO9521607; WO9629992; WO9633700; WO9640080; WO9748386; WO9833488; WO9833489; WO9930692; WO9947125; and WO9961005.

Some other examples of drug delivery approaches focus on non-oral drug delivery, providing parenteral, transmucosal, and topical delivery of proteins, peptides, and small molecules. For example, the Atrigel® drug delivery system marketed by Atrix Laboratories Inc. comprises biodegradable polymers, similar to those used in biodegradable sutures, dissolved in biocompatible carriers. These pharmaceuticals may be blended into a liquid delivery system at the time of manufacturing or, depending upon the product, may be added later by a physician at the time of use. Injection of the liquid product subcutaneously or intramuscularly through a small gauge needle, or placement into accessible tissue sites through a cannula, causes displacement of the carrier with water in the tissue fluids, and a subsequent precipitate to form from the polymer into a solid film or implant. The drug encapsulated within the implant is then released in a controlled manner as the polymer matrix biodegrades over a period ranging from days to

months. Examples of such drug delivery systems include Atrix's Eligard®, Atridox®/ Doxirobe®, Atrisorb® FreeFlow™/ Atrisorb®-D FreeFlow, bone growth products, and others as described in the following published US and PCT patent applications assigned to Atrix Laboratories Inc.: US RE37950; US 6,630,155; US 6,566,144; US 6,610,252; US 6,565,874; US 6,528,080; US 6,461,631; US 6,395,293; US 6,261,583; US 6,143,314; US 6,120,789; US 6,071,530; US 5,990,194; US 5,945,115; US 5,888,533; US 5,792,469; US 5,780,044; US 5,759,563; US 5,744,153; US 5,739,176; US 5,736,152; US 5,733,950; US 5,702,716; US 5,681,873; US 5,660,849; US 5,599,552; US 5,487,897; US 5,368,859; US 5,340,849; US 5,324,519; US 5,278,202; US 5,278,201; US20020114737, US20030195489; US20030133964;US 20010042317; US20020090398; US20020001608; and US2001042317.

Atrix Laboratories Inc. also markets technology for the non-oral transmucosal delivery of drugs over a time period from minutes to hours. For example, Atrix's BEMA™ (Bioerodible Muco-Adhesive Disc) drug delivery system comprises pre-formed bioerodible discs for local or systemic delivery. Examples of such drug delivery systems include those as described in US Patent No. 6,245,345.

Other drug delivery systems marketed by Atrix Laboratories Inc. focus on topical drug delivery. For example, SMP™ (Solvent Particle System) allows the topical delivery of highly water-insoluble drugs. This product allows for a controlled amount of a dissolved drug to permeate the epidermal layer of the skin by combining the dissolved drug with a microparticle suspension of the drug. The SMP™ system works in stages whereby: 1) the product is applied to the skin surface; 2) the product near follicles concentrates at the skin pore; 3) the drug readily partitions into skin oils; and 4) the drug diffuses throughout the area. By contrast, MCA® (Mucocutaneous Absorption System) is a water-resistant topical gel providing sustained drug delivery. MCA® forms a tenacious film for either wet or dry surfaces where: 1) the product is applied to the skin or mucosal surface; 2) the product forms a tenacious moisture-resistant film; and 3) the adhered film provides sustained release of drug for a period from hours to days. Yet another product, BCP™ (Biocompatible Polymer System) provides a non-cytotoxic gel or liquid that is applied as a protective film for wound healing. Examples of these systems include Orajel®-Ultra Mouth Sore Medicine as well as those as described in the following

published US patents and applications assigned to Atrix Laboratories Inc.: US 6,537,565; US 6,432,415; US 6,355,657; US 5,962,006; US 5,725,491; US 5,722,950; US 5,717,030; US 5,707,647; US 5,632,727; and US20010033853.

Dosage and Administration

The concentration of the active agent in any of the aforementioned dosage forms and compositions can vary a great deal, and will depend on a variety of factors, including the type of composition or dosage form, the corresponding mode of administration, the nature and activity of the specific active agent, and the intended drug release profile. Preferred dosage forms contain a unit dose of active agent, i.e., a single therapeutically effective dose. For creams, ointments, etc., a "unit dose" requires an active agent concentration that provides a unit dose in a specified quantity of the formulation to be applied. The unit dose of any particular active agent will depend, of course, on the active agent and on the mode of administration.

For the active agents of the present invention (including an $\alpha_2\delta$ subunit calcium channel modulator in combination with a compound with smooth muscle modulatory effects), the unit dose for oral, transmucosal, topical, transdermal, and parenteral administration will be in the range of from about 1 ng to about 10,000 mg, typically in the range of from about 100 ng to about 5,000 mg. Alternatively, for active agents of the present invention (including an $\alpha_2\delta$ subunit calcium channel modulator in combination with a compound with smooth muscle modulatory effects), the unit dose for oral, transmucosal, topical, transdermal, and parenteral administration will be greater than about 1 ng, about 5 ng, about 10 ng, about 20 ng, about 30 ng, about 40 ng, about 50 ng, about 100 ng, about 200 ng, about 300 ng, about 400 ng, about 500 ng, about 1 μg, about 5 μg, about 10 μg, about 20 μg, about 30 μg, about 40 μg, about 50 μg, about 100 μg, about 200 μg, about 300 μg, about 400 μg, about 500 μg, about .5 mg, about 1 mg, about 1.5 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 4.0 mg, about 4.5 mg, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg,

about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 3,000 mg, about 3,500 mg, about 4,000 mg, about 4,500 mg, about 5,000 mg, about 5,500 mg, about 6,000 mg, about 6,500 mg, about 7,000 mg, about 7,500 mg, about 8,000 mg, about 8,500 mg, about 9,000 mg, or about 9,500 mg.

For the active agents of the present invention (including an $\alpha_2\delta$ subunit calcium channel modulator in combination with a compound with smooth muscle modulatory effects), the unit dose for intrathecal administration will be in the range of from about 1 fg to about 1 mg, typically in the range of from about 100 fg to about 1 ng. Alternatively, for the active agents of the present invention (including an $\alpha_2\delta$ subunit calcium channel modulator in combination with a compound with smooth muscle modulatory effects), the unit dose for intrathecal administration will be greater than about 1 fg, about 5 fg, about 10 fg, about 20 fg, about 30 fg, about 40 fg, about 50 fg, about 100 fg, about 200 fg, about 300 fg, about 400 fg, about 500 fg, about 1 pg, about 5 pg, about 10 pg, about 20 pg, about 30 pg, about 40 pg, about 50 pg, about 100 pg, about 200 pg, about 300 pg, about 400 pg, about 500 pg, about 1 ng, about 5 ng, about 10 ng, about 20 ng, about 30 ng, about 40 ng, about 50 ng, about 100 ng, about 200 ng, about 300 ng, about 400 ng, about 500 ng, about 1 μg, about 5 μg, about 10 μg, about 20 μg, about 30 μg, about 40 μg, about 50 μg, about 100 μg, about 200 μg, about 300 μg, about 400 μg, or about 500 μg.

The present invention also encompasses a pharmaceutical formulation encompassing oxybutyinin, wherein the unit dose for oral, transmucosal, topical, transdermal, and parenteral administration of said oxybutynin will be in an amount less than about 5 mg, less than about 4.5 mg, less than about 4 mg, less than about 3.5 mg, less than about 3 mg, less than about 2.5 mg, less than about 2 mg, less than about 1.5 mg, or less than about .5 mg.

A therapeutically effective amount of a particular active agent administered to a given individual will, of course, be dependent on a number of factors, including the concentration of the specific active agent, composition or dosage form, the selected mode of administration, the age and general condition of the individual being treated, the severity of the individual's condition, and other factors known to the prescribing physician.

In a preferred embodiment, drug administration is on an as-needed basis, and does not involve chronic drug administration. With an immediate release dosage form, as-needed administration may involve drug administration immediately prior to commencement of an activity wherein suppression of the symptoms of overactive bladder would be desirable, but will generally be in the range of from about 0 minutes to about 10 hours prior to such an activity, preferably in the range of from about 0 minutes to about 5 hours prior to such an activity, most preferably in the range of from about 0 minutes to about 3 hours prior to such an activity. With a sustained release dosage form, a single dose can provide therapeutic efficacy over an extended time period in the range of from about 1 hour to about 72 hours, typically in the range of from about 8 hours to about 48 hours, depending on the formulation. That is, the release period may be varied by the selection and relative quantity of particular sustained release polymers. If necessary, however, drug administration may be carried out within the context of an ongoing dosage regimen, i.e., on a weekly basis, twice weekly, daily, etc.

Packaged Kits

In another embodiment, a packaged kit is provided that contains the pharmaceutical formulation to be administered, i.e., a pharmaceutical formulation containing a therapeutically effective amount of an $\alpha_2\delta$ subunit calcium channel

modulator in combination with one or more compounds with smooth muscle modulatory effects for the treatment of painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients, a container, preferably sealed, for housing the formulation during storage and prior to use, and instructions for carrying out drug administration in a manner effective to treat painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. The instructions will typically be written instructions on a package insert and/or on a label. Depending on the type of formulation and the intended mode of administration, the kit may also include a device for administering the formulation. The formulation may be any suitable formulation as described herein. For example, the formulation may be an oral dosage form containing a unit dosage of a selected active agent. The kit may contain multiple formulations of different dosages of the same agent. The kit may also contain multiple formulations of different active agents.

Many modifications and other embodiments of the inventions set forth herein will come to mind to one skilled in the art to which these inventions pertain having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the inventions are not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended embodiments. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Insurance Claims

In general, the processing of an insurance claim for the coverage of a given medical treatment or drug therapy involves notification of the insurance company, or any other entity, that has issued the insurance policy against which the claim is being filed,

that the medical treatment or drug therapy will be performed. A determination is then made as to whether the medical treatment or drug therapy that will be performed is covered under the terms of the policy. If covered, the claim is then processed, which can include payment, reimbursement, or application against a deductable.

The present invention encompasses a method for processing an insurance claim under an insurance policy for an $\alpha_2\delta$ subunit calcium channel modulator and an antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof used in the treatment of lower urinary tract disorders, wherein said $\alpha_2\delta$ subunit calcium channel modulator and antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof are administered sequentially or concurrently in different compositions. This method comprises: 1) receiving notification that treatment using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs or active metabolites thereof will be performed or notification of a prescription; 2) determining whether said treatment using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs or active metabolites is covered under said insurance policy; and 3) processing said claim for treatment of said lower urinary tract disorders using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof, including payment, reimbursement, or application against a deductable. For use in this method, a particularly preferred $\alpha_2\delta$ subunit calcium channel modulator is gabapentin, while a particularly preferred antimuscarinic is oxybutynin. This method also encompasses the processing of claims for and $\alpha_2\delta$ subunit calcium channel modulator, particularly gabapentin, or an antimuscarinic, particularly oxybutynin, when either has been prescribed separately or concurrently for the treatment of lower urinary tract disorders.

EXAMPLES

Methods For Treating Lower Urinary Tract Disorders Using $\alpha_2\delta$ Subunit Calcium Channel Modulators With Smooth Muscle Modulators

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims. The following examples illustrate the effects of administration of the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator on bladder capacity in an irritated bladder model. It is expected that these results will demonstrate the efficacy of the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator for treatment of painful and non-painful lower urinary tract disorders and the related disorders vulvodynia and vulvar vestibulitis in normal and spinal cord injured patients as described herein.

These methods include the use of a well accepted model of for urinary tract disorders involving the bladder using intravesically administered acetic acid as described in Sasaki *et al.* (2002) *J. Urol.* 168: 1259-64. Efficacy for treating spinal cord injured patients can be tested using methods as described in Yoshiyama *et al.* (1999) Urology 54: 929-33.

The present invention encompasses the use of antimuscarinics except for atropine, scopolomine, and trospium chloride. It is noted that each of these compounds all contain an amine embedded in an 8-azabicyclo[3.2.1]octan-3-ol skeleton.

Example 1 – Gabapentin and Oxybutynin

Objective and Rationale

The objective of this study was to determine the effect of combining oxybutynin, a musculotropic drug and smooth muscle modulator with gabapentin, a neurotropic drug and $\alpha_2\delta$ subunit calcium channel modulator, on the ability to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder.

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with oxybutynin alone (n=8), gabapentin alone (n=5), and respective dose–matched combinations of oxybutynin and gabapentin (n=3). Subsequently, three series at markedly lower doses and at different dose ratios were

performed for the purposes of isobologram construction (n=3-4/group). Cumulative dose-response protocols were utilized with half log increments for all studies. A total of 27 rats were utilized for this investigation.

Drugs and Preparation

Drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for oxybutynin and 30, 100 and 300 mg/ml for gabapentin. Subsequent studies aimed at isobologram construction combined the drugs in dose combinations as shown in the table below (low, middle and high doses for each drug paired). Animals were dosed by volume of injection = body weight in kg.

Table: Isobologram Dose Combinations (mg/kg)

Isobologram Dose Combinations	Isobologram 1	Isobologram 2	Isobologram 3
Oxybutynin	0.1, 0.3, 1.0	0.1, 0.3, 1.0	0.03, 0.1, 0.3
Gabapentin	1.0, 3.0, 10.0	3.0, 10.0, 30.0	3.0, 10.0, 30.0

Acute Anesthetized In Vivo Model

Animal Preparation: Female rats (250-275 g body weight) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying

purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design - Dilute Acetic Acid Model: Saline was continuously infused at a rate of 0.055 ml/min via the bladder-filling catheter for 60 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a 0.25% acetic acid solution in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity caused by the irritation protocol and subsequent intravesical drug administration.

Data Analysis

Data were analyzed by non-parametric ANOVA for repeated measures (Friedman Test) with Dunn's Multiple Comparison test for cumulative dose-response studies and the Mann Whitney t test for single dose comparisons. All comparisons were made from the last vehicle measurement. $P<0.050$ was considered significant.

Isobologram construction consisted of two methods, both utilizing the same data, but plotting the results either as group means or by individual responses. When utilizing group mean data, the common maximal effect reached by both drugs alone and the combinations listed in the above table was a return to 43% of saline control bladder capacity values. When utilizing individual responses for both drugs alone and the combinations listed in the above table, the target value was 31% of saline control. These low values reflect the modest effectiveness of oxybutynin and gabapentin alone. For

statistical purposes, the data were analyzed making comparisons for each drug, regardless of whether alone or in combination.

For the purposes of determining synergistic effects with statistical analysis backing utilizing all of the data simultaneously, a strategy was devised that utilized the actual data from the oxybutynin and gabapentin alone experiments to create a population of all possible additive results that can be generated from these data for each dose (low, mid and high) and these were compared by t test to the actual combination data.

Results

Figure Legends

Figure 1: Graphic depiction of the effect of cumulative increasing doses of oxybutynin (n=8), gabapentin (n=5) and their matched combinations (e.g. Dose 1 for the combination was 30 mg/kg gabapentin and 1 mg/kg oxybutynin). Note the robust effect seen with the dose-matched combination of the two drugs as compared their individual administration on reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid.

Figure 2: Graphic depiction of the results of the isobologram studies as determined by utilizing group means to determine effective doses. Using this technique, the common maximal effect for either drug alone was return to 43% of saline control. The line connecting the two axes at the effective dose for each drug alone represents theoretical additivity. The three isolated points clustered in the lower left field of the graph below the line of additivity represent the dose ranges from three sets of experiments utilizing low-dose ratios of drug combinations. As can be readily visualized by this isobologram, significantly lower doses of both drugs were required in combination to achieve the same endpoint as either drug alone.

Figure 3: In an attempt to give statistical validity to the isobologram studies, a common maximal effect of individual animals was determined (a return to 31% of

saline control values). Using this approach, it was possible to show that no overlap existed between the doses of oxybutynin alone and those used in the isobologram combination studies in terms of standard deviation, and that all effective combination ranges of oxybutynin were significantly lower than the range of oxybutyin alone. Similarly, the effective ranges of gabapentin used in the combinations were significantly lower than when gabapentin was used alone.

Figure 4: In a further attempt to demonstrate synergistic rather than additive effects statistically, bladder capacity data from the original study were normalized to irritated values. The above graph shows the results of that normalization. As seen previously, the dose-matched combination of the two drugs was significantly more efficacious than either drug alone. However, this alone did not prove synergy. Note that there were no significant differences between any of the saline measures.

When the individual differences from irritated values (AA/Veh 3) were calculated for each experiment at each dose, it was possible to construct a simple 8 x 5 grid of possible additivity based upon the real data from the animals treated with single drug alone (n=8 for oxybutynin, n=5 for gabapentin). The resultant population of expected additive effects was then utilized to compare to the actual combination data in a dose-matched fashion. The resultant statistical analyses proved that the combinations were synergistic at all doses (Figures 5-7).

Figure 5: Graphic depiction of calculated additivity results (see description above) and the actual combination results at Dose 1 for both drugs. Statistical analysis reveals that the Dose 1 combination is significantly higher in value than that of the calculated additive population for that combination.

Figure 6: Graphic depiction of calculated additivity results (see description above) and the actual combination results at Dose 2 for both drugs. Statistical

analysis reveals that the Dose 2 combination is significantly higher in value than that of the calculated additive population for that combination.

Figure 7: Graphic depiction of calculated additivity results (see description above) and the actual combination results at Dose 3 for both drugs. Statistical analysis reveals that the Dose 3 combination is significantly higher in value than that of the calculated additive population for that combination.

Figure 1

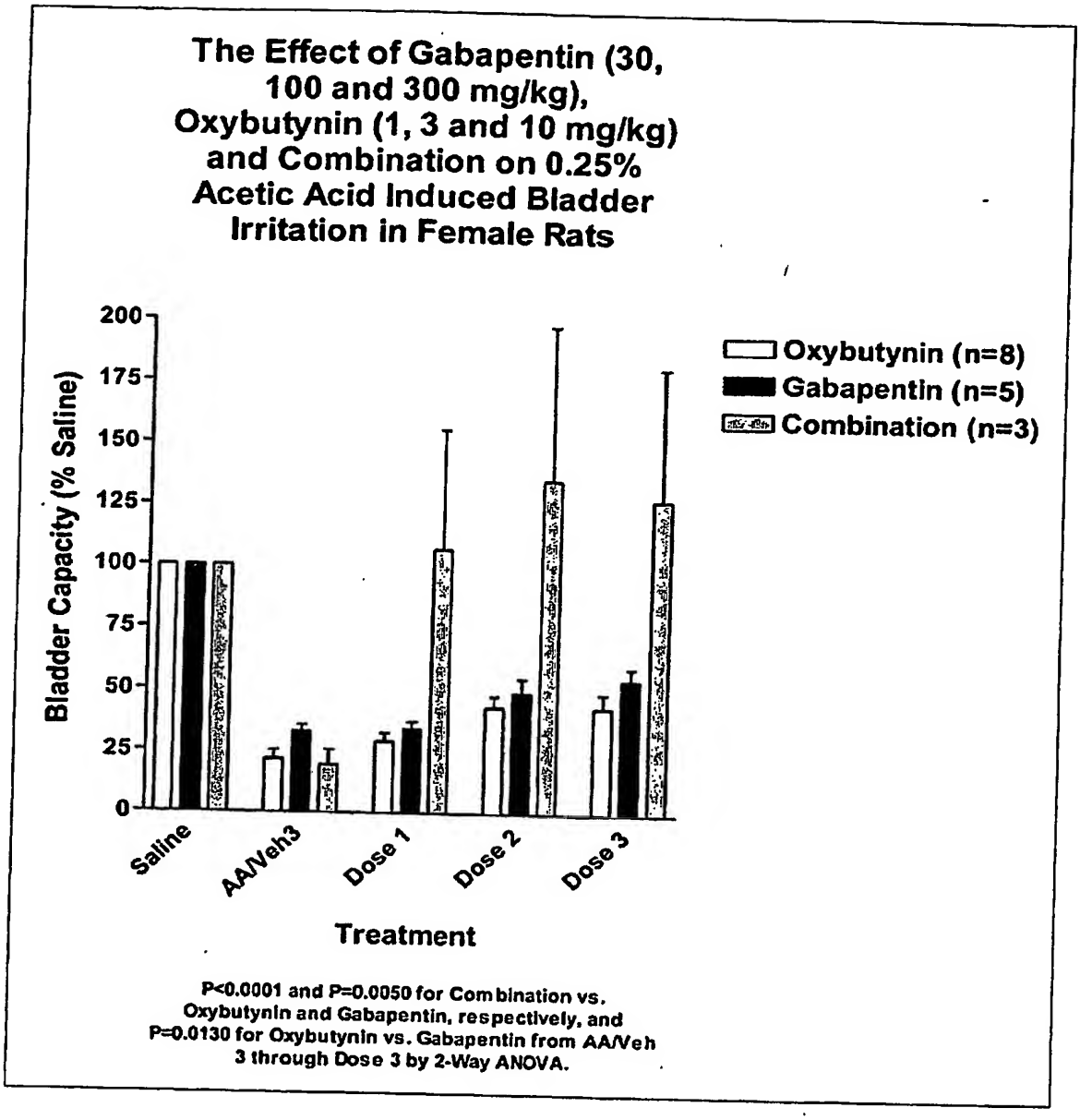

The Effect of Gabapentin (30, 100 and 300 mg/kg), Oxybutynin (1, 3 and 10 mg/kg) and Combination on 0.25% Acetic Acid Induced Bladder Irritation in Female Rats
Bladder Capacity (% Saline)
200
175
150
125
100
75
50
25
0
Saline
AA/Veh3
Dose 1
Dose 2
Dose 3
Treatment
Oxybutynin (n=8)
Gabapentin (n=5)
Combination (n=3)
P<0.0001 and P=0.0050 for Combination vs. Oxybutynin and Gabapentin, respectively, and P=0.0130 for Oxybutynin vs. Gabapentin from AA/Veh 3 through Dose 3 by 2-Way ANOVA.

Figure 2

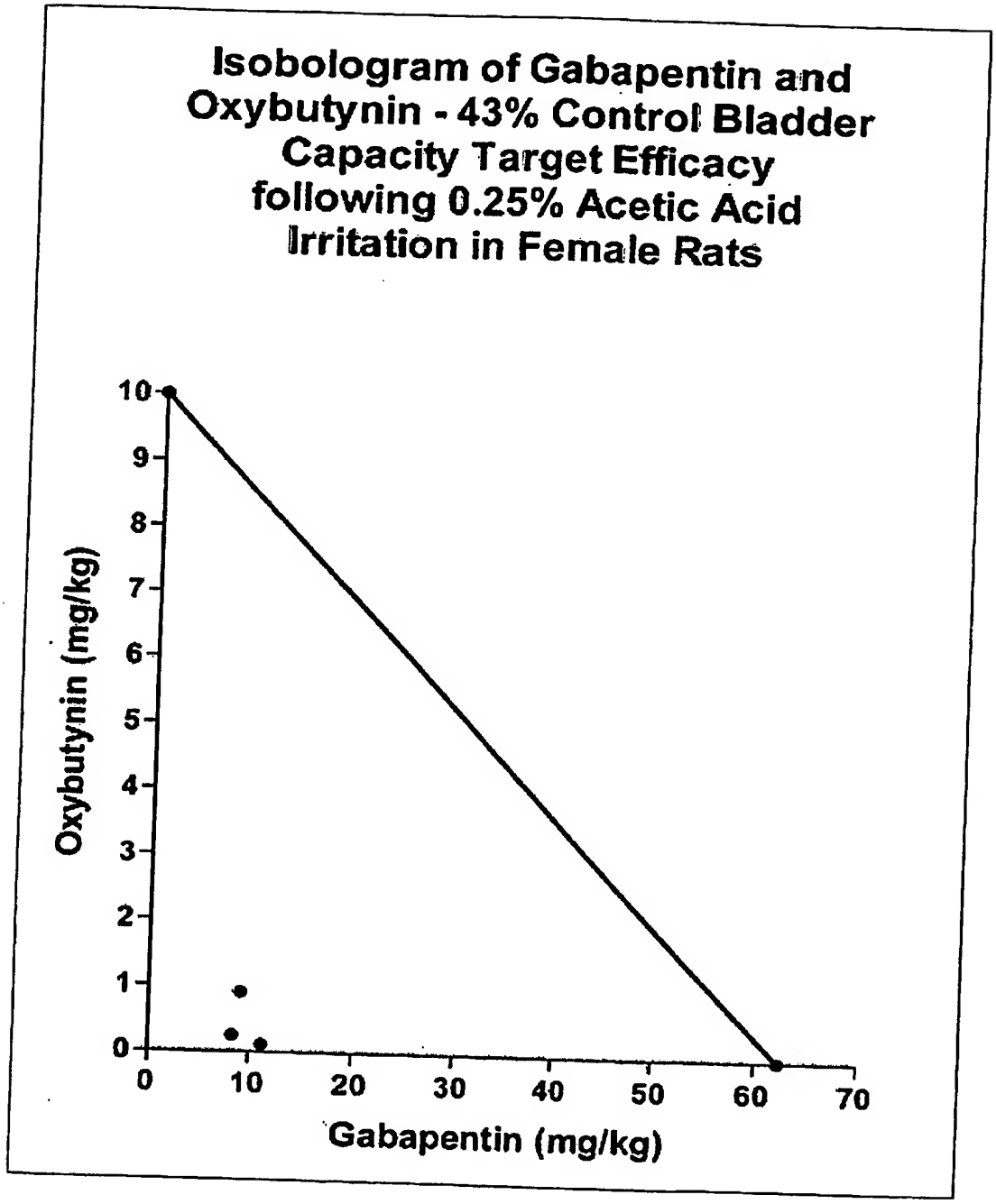

Isobologram of Gabapentin and Oxybutynin - 43% Control Bladder Capacity Target Efficacy following 0.25% Acetic Acid Irritation in Female Rats
Oxybutynin (mg/kg)
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60
70
Gabapentin (mg/kg)

Figure 3

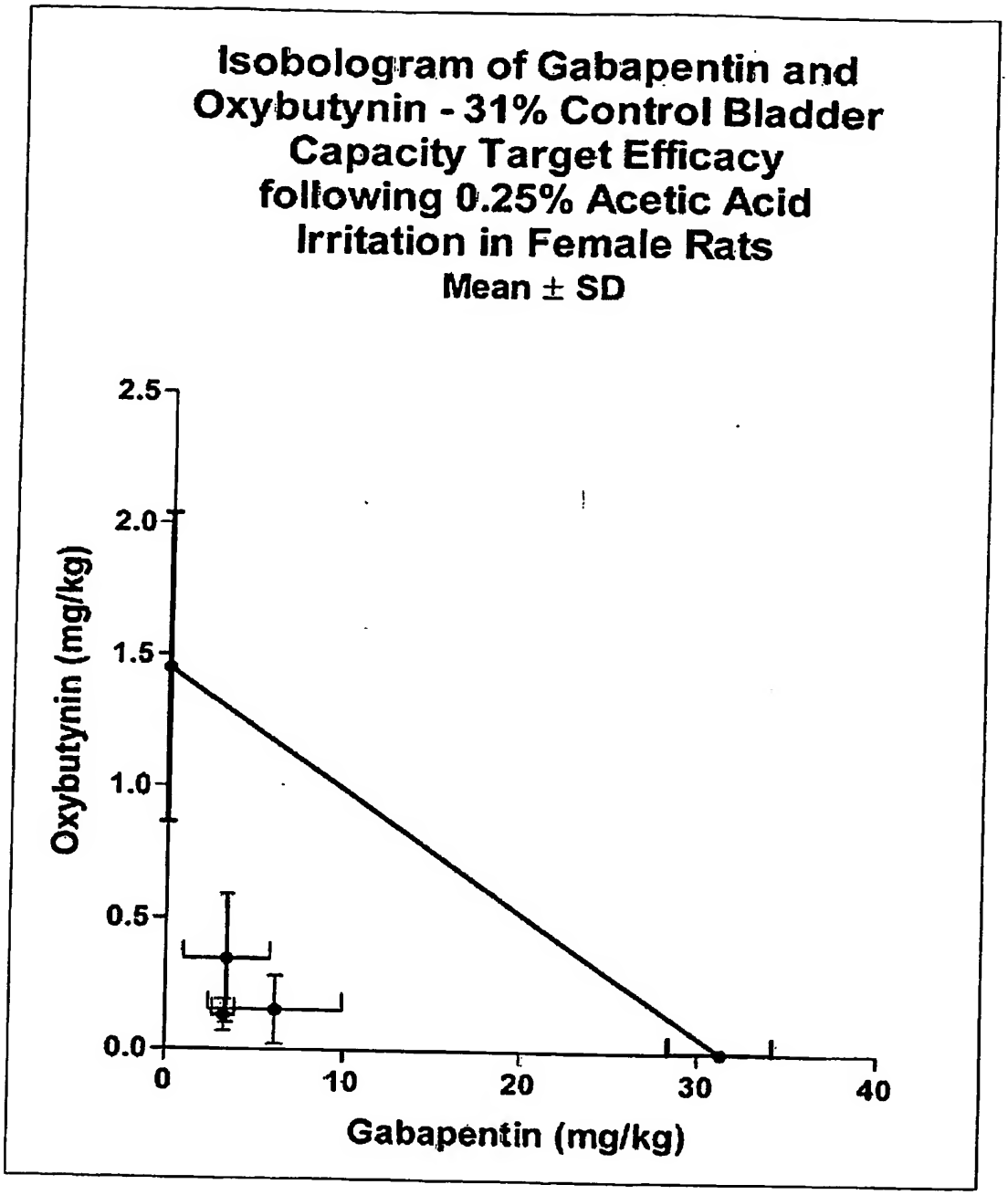

Isobologram of Gabapentin and Oxybutynin - 31% Control Bladder Capacity Target Efficacy following 0.25% Acetic Acid Irritation in Female Rats
Mean ± SD
Oxybutynin (mg/kg)
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
Gabapentin (mg/kg)

Figure 4

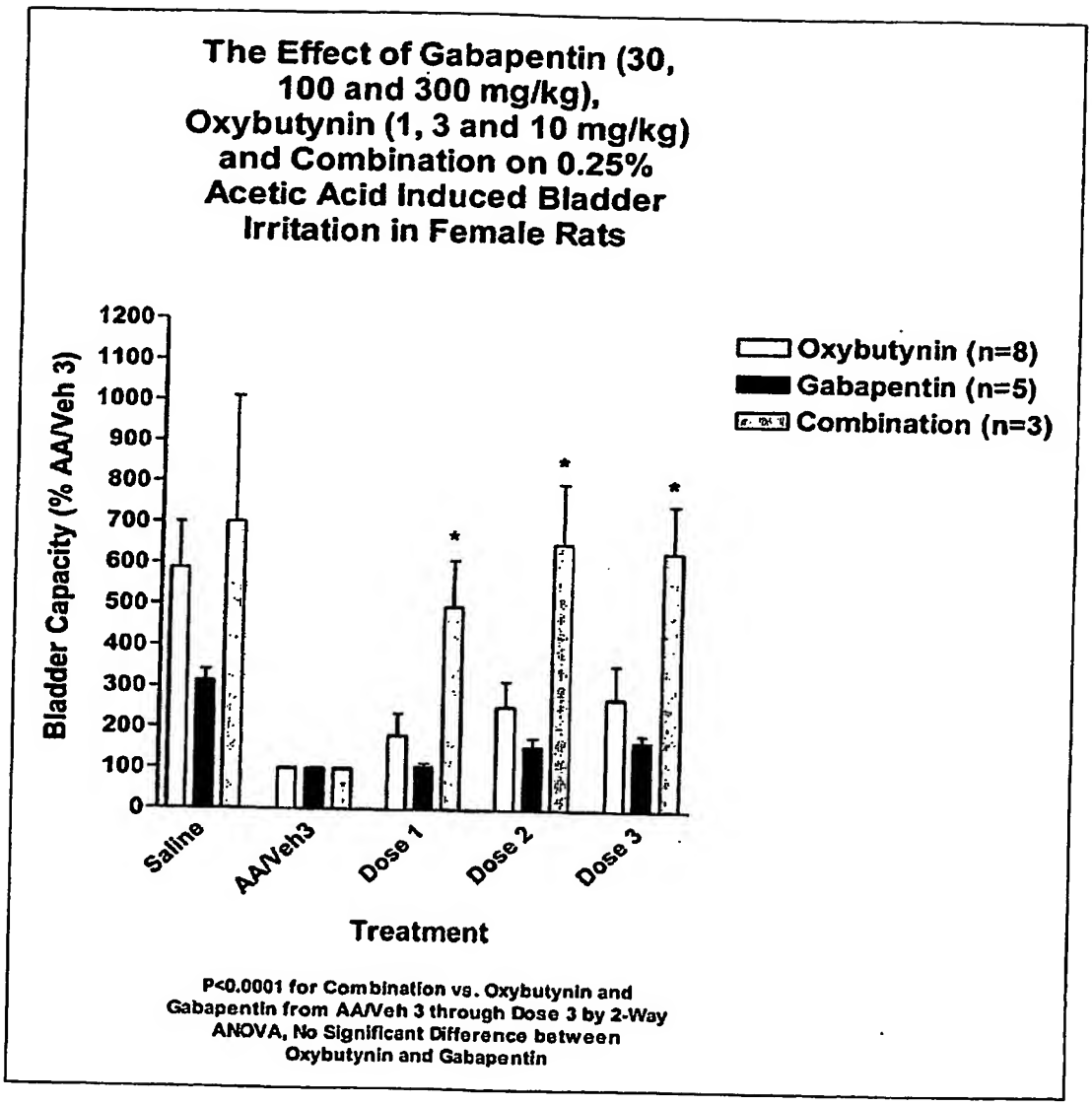

The Effect of Gabapentin (30, 100 and 300 mg/kg), Oxybutynin (1, 3 and 10 mg/kg) and Combination on 0.25% Acetic Acid Induced Bladder Irritation in Female Rats
Bladder Capacity (% AA/Veh 3)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Saline
AA/Veh3
Dose 1
Dose 2
Dose 3
Treatment
Oxybutynin (n=8)
Gabapentin (n=5)
Combination (n=3)
P<0.0001 for Combination vs. Oxybutynin and Gabapentin from AA/Veh 3 through Dose 3 by 2-Way ANOVA, No Significant Difference between Oxybutynin and Gabapentin

Figure 5

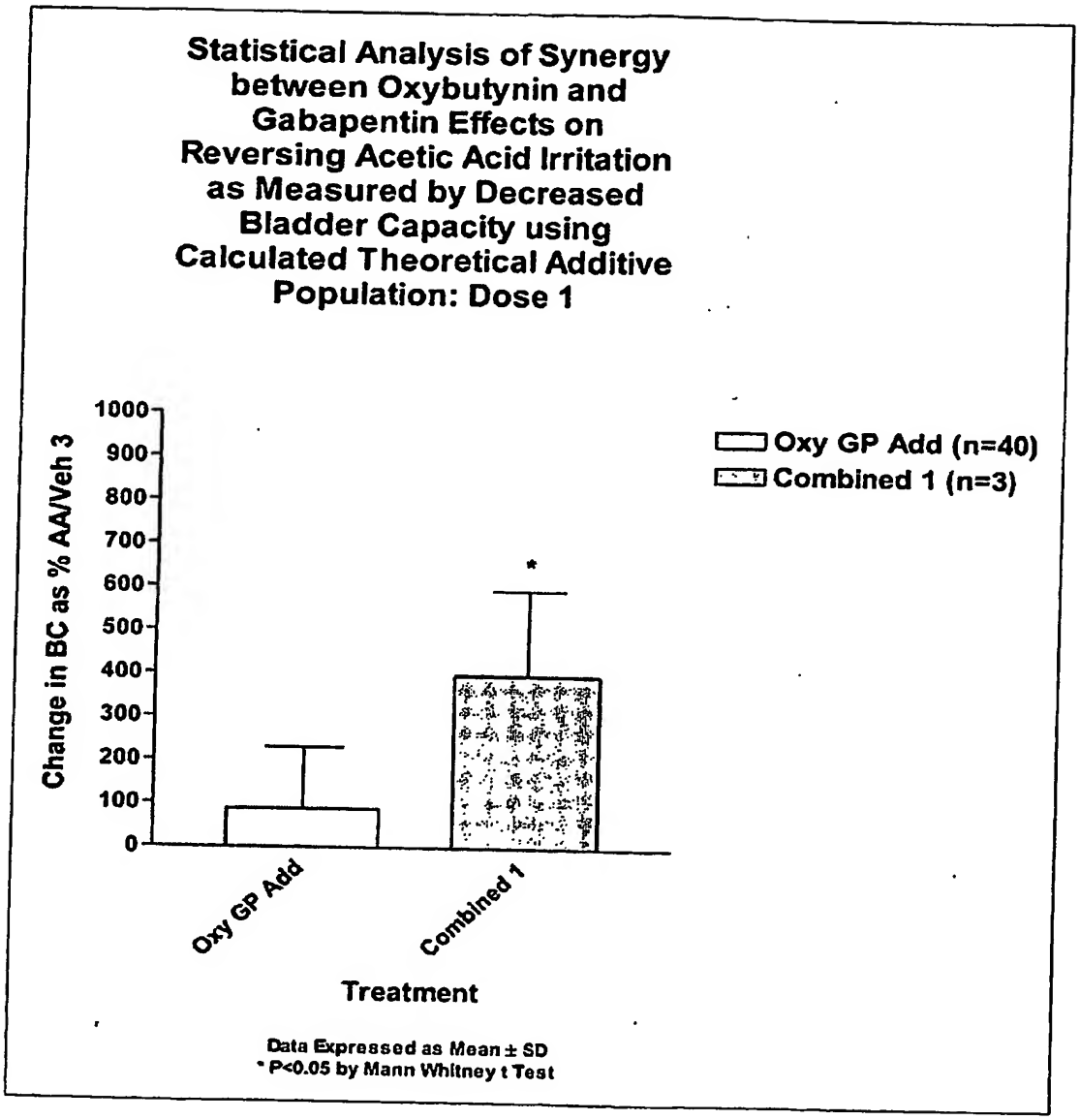

Statistical Analysis of Synergy between Oxybutynin and Gabapentin Effects on Reversing Acetic Acid Irritation as Measured by Decreased Bladder Capacity using Calculated Theoretical Additive Population: Dose 1
Change in BC as % AA/Veh 3
1000
900
800
700
600
500
400
300
200
100
0
*
Oxy GP Add (n=40)
Combined 1 (n=3)
Oxy GP Add
Combined 1
Treatment
Data Expressed as Mean ± SD
* P<0.05 by Mann Whitney t Test

Figure 6

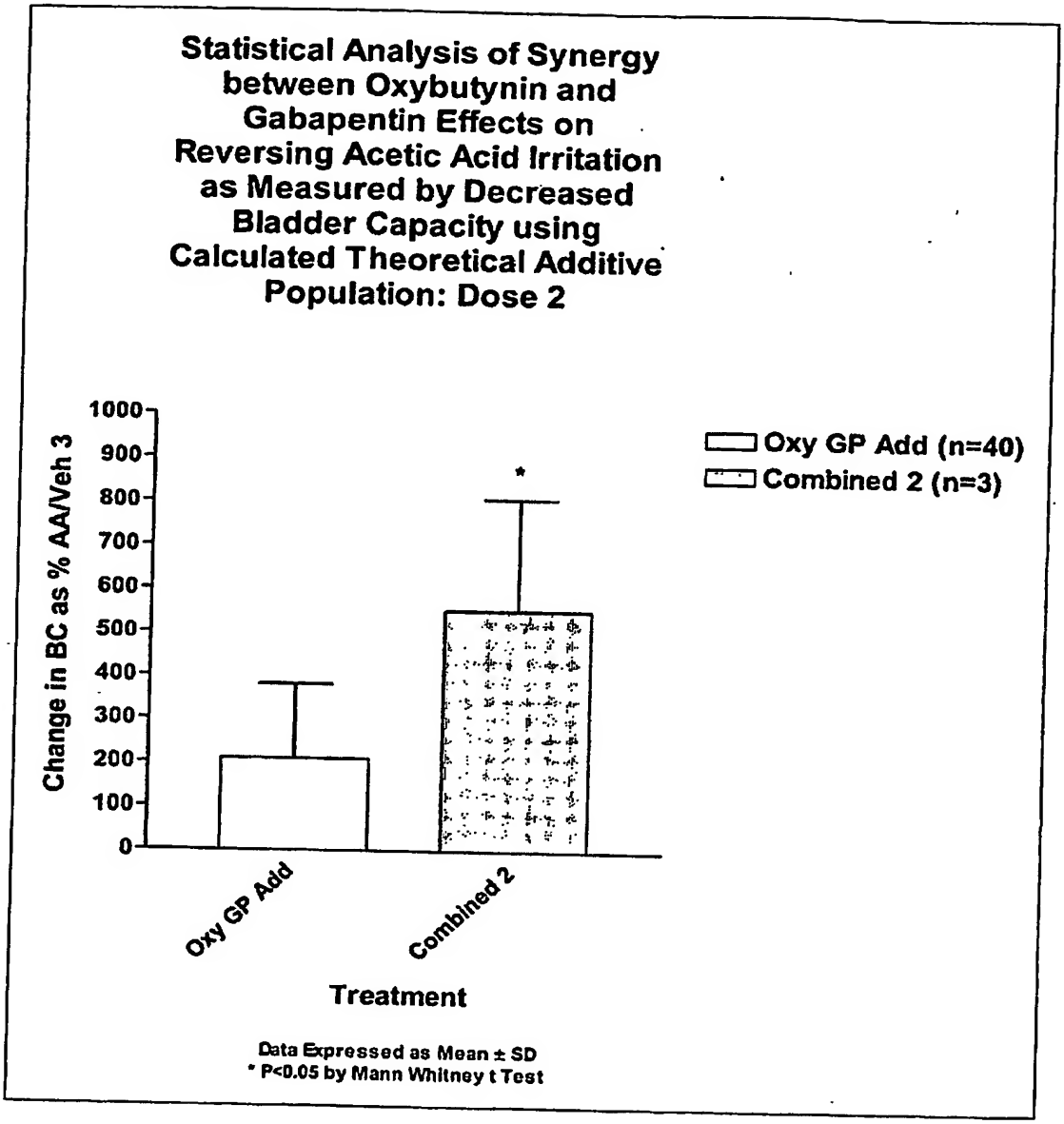
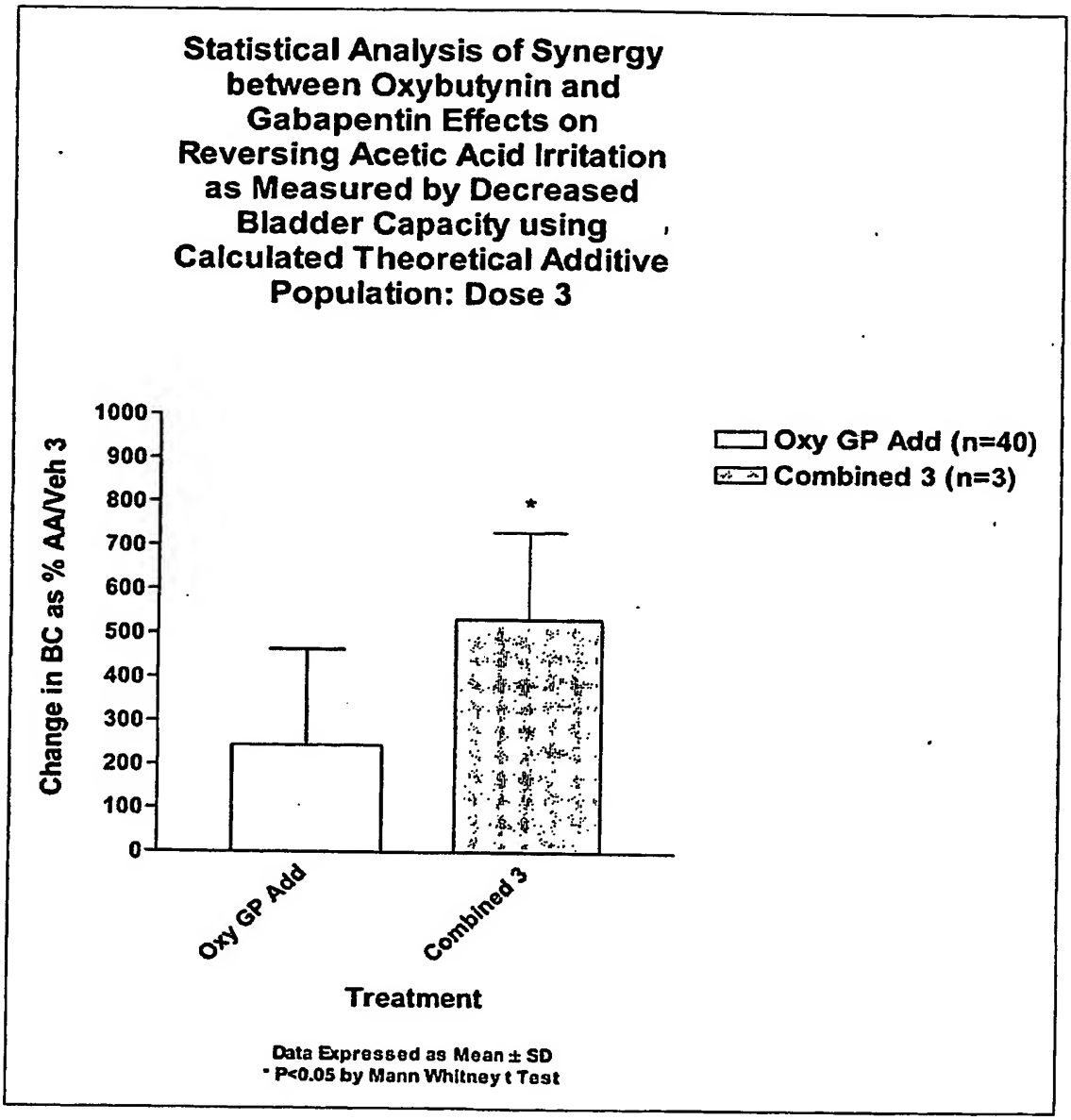

Statistical Analysis of Synergy between Oxybutynin and Gabapentin Effects on Reversing Acetic Acid Irritation as Measured by Decreased Bladder Capacity using Calculated Theoretical Additive
Population: Dose 2
Change in BC as % AA/Veh 3
1000
900
800
700
600
500
400
300
200
100
0
*
Oxy GP Add (n=40)
Combined 2 (n=3)
Oxy GP Add
Combined 2
Treatment
Data Expressed as Mean ± SD
* P<0.05 by Mann Whitney t Test

Figure 7


Statistical Analysis of Synergy between Oxybutynin and Gabapentin Effects on Reversing Acetic Acid Irritation as Measured by Decreased Bladder Capacity using Calculated Theoretical Additive Population: Dose 3
Change in BC as % AA/Veh 3
1000
900
800
700
600
500
400
300
200
100
0
*
Oxy GP Add (n=40)
Combined 3 (n=3)
Oxy GP Add
Combined 3
Treatment
Data Expressed as Mean ± SD
* P<0.05 by Mann Whitney t Test

Conclusions

While oxybutynin and gabapentin alone were capable of partially reversing the reduction in bladder capacity caused by continuous infusion of dilute acetic acid, the combination of the two allowed for full reversal of the irritation effect. Both by isobolgram-based approaches and by construction of theoretical populations of possible additive effects at each dose, statistical analyses revealed that the combination of the two drugs produced a synergistic effect that was greater than what would be expected if the effects were simply additive.

Example 2 – Gabapentin and Tolterodine

Objective and Rationale

The objective of this study was to determine the effect of combining tolterodine, a musculotropic drug and smooth muscle modulator with gabapentin, a neurotropic drug and $\alpha_2\delta$ subunit calcium channel modulator, on the ability to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder.

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with tolterodine alone (n=5) and gabapentin alone (n=5). Because tolterodine alone had no effect on bladder capacity in this model, an isobologram could not be constructed. As a first step in determining synergy, it was assumed that a single dose of tolterodine in combination with the first dose of the gabapentin dose response would allow for synergy determination. Cumulative dose-response protocols utilized with half log increments for all studies. Doses of tolterodine for single administration during synergy studies were identical to those used in the tolterodine alone dose response (n=3-4 per group). A total of 21 rats were utilized for generating this report.

Drugs and Preparation

Drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for tolterodine and 30, 100 and 300 mg/ml for gabapentin. Animals were dosed by volume of injection = body weight in kg.

Acute Anesthetized In Vivo Model

Animal Preparation: Female rats (250-275 g body weight) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design - Dilute Acetic Acid Model : Saline was continuously infused at a rate of 0.055 ml/min via the bladder filling catheter for 60 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a 0.25% acetic acid solution in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity caused by the irritation protocol and subsequent intravesical drug administration.

Data Analysis

Bladder capacity was estimated by using the greater of either intermicturition interval or single filling cystometry. Data were analyzed by non-parametric ANOVA for repeated measures (Friedman Test) with Dunn's Multiple Comparison test for cumulative dose-response studies and the Mann Whitney t test for single dose comparisons. All comparisons were made from the last vehicle measurement. $P<0.050$ was considered significant.

For the purposes of statistically proving synergy, a strategy was devised that utilized the data from the tolterodine and gabapentin alone experiments to create a population of all possible additive results that can be generated from these data for the low dose, and these were compared by t test to the actual combination data. In the case of these experiments, a population of 25 summed values was generated from 5 oxybutynin and 5 gabapentin data points for the low dose.

Results

Figure Legends

Figure 8: Graphic depiction of the effect of cumulative increasing doses of tolterodine (1, 3 and 10 mg/kg; n=5) and gabapentin (30, 100 and 300 mg/kg; n=5). Note that tolterodine alone had no effect on the reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid, while gabapentin alone had a modest effect. Data have been normalized to irritated control values (AA/Veh 3) and are presented as Mean ± SEM.

Figure 9: Graphic depiction of the effect of single dose administration of tolterodine at three different doses (1, 3 and 10 mg/kg; n=4, 4 and 3, respectively) along with the first dose of a gabapentin cumulative dose response (30, 100 and 300 mg/kg). Note that addition of tolterodine resulted in an enhancement of the gabapentin low dose response. Data have been normalized to irritated control values (AA/Veh 3) and are presented as Mean ± SEM.

When the individual differences from irritated values (AA/Veh 3) were calculated for each experiment at each dose, it was possible to construct a simple 5 x 5 grid of possible additivity based upon the real data from the animals treated with single drug alone (n=5 for tolterodine, n=5 for gabapentin). The resultant population of expected additive effects was then utilized to compare to the actual combination data in a dose-matched fashion. The resultant statistical analyses proved that the mid and high doses of tolterodine in combination with the low dose of gabapentin were synergistic (Figure 10).

Figure 10: Graphic depiction of calculated additivity results (see description above) and the actual combination results at for both drugs. Statistical analysis reveals that the 3 and 10 mg/kg dose of tolterodine, when co-administered with 30 mg/kg gabapentin, resulted in significantly higher values than those of the calculated additive population. Data are presented as Mean ± SD.

Figure 8

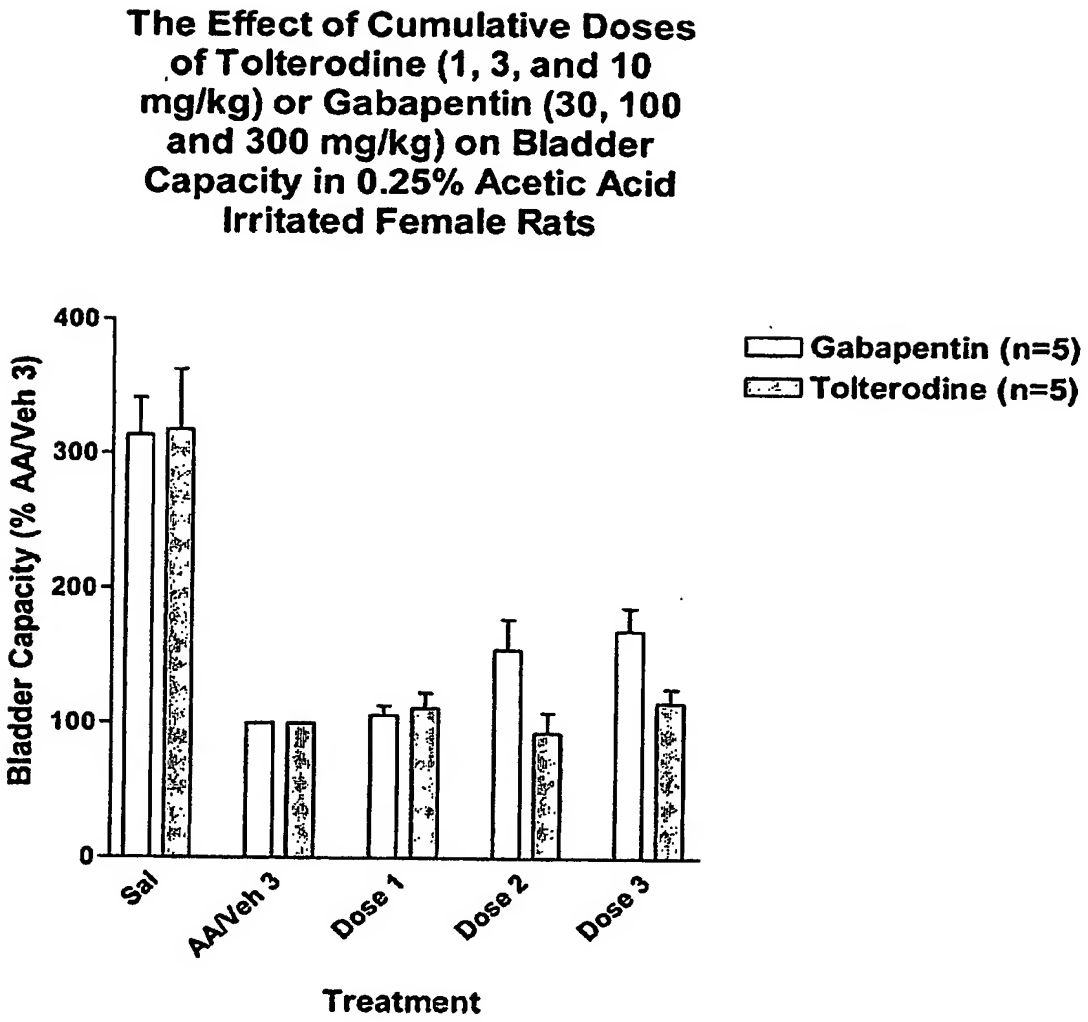

The Effect of Cumulative Doses of Tolterodine (1, 3, and 10 mg/kg) or Gabapentin (30, 100 and 300 mg/kg) on Bladder Capacity in 0.25% Acetic Acid Irritated Female Rats
Bladder Capacity (% AA/Veh 3)
400
300
200
100
0
Sal
AA/Veh 3
Dose 1
Dose 2
Dose 3
Treatment
Gabapentin (n=5)
Tolterodine (n=5)

Figure 9

The Effect of Low Doses of Tolterodine (1 mg/kg) and Gabapentin (30 mg/kg), and Different Doses of Tolterodine in Combination with Gabapentin, on Bladder Capacity in 0.25% Acetic Acid Irritated Female Rats

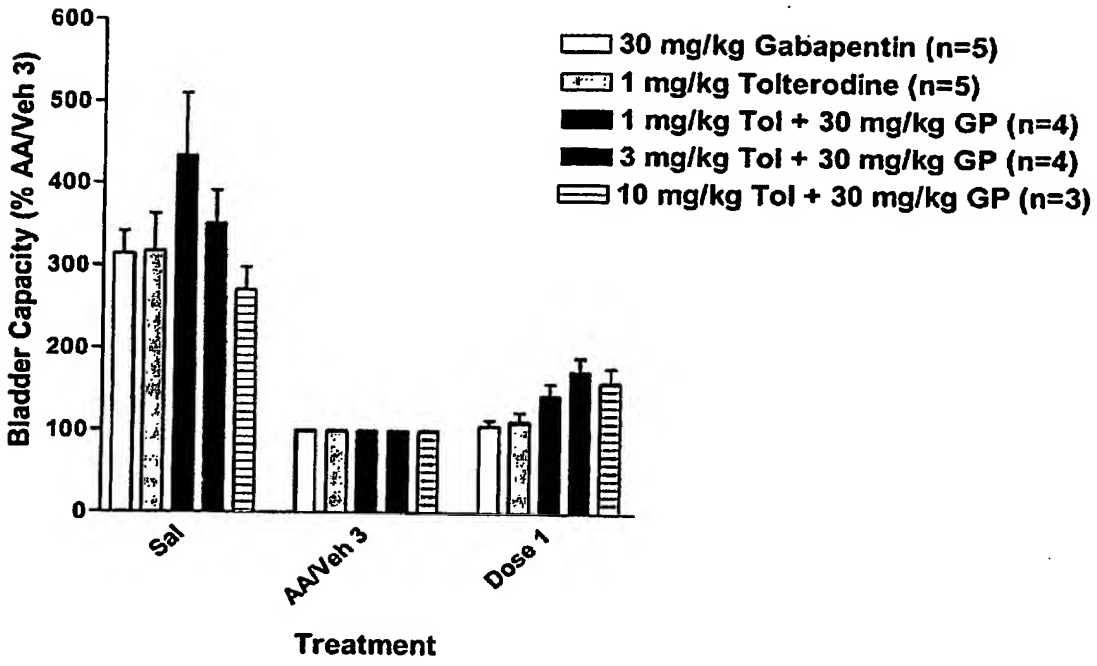
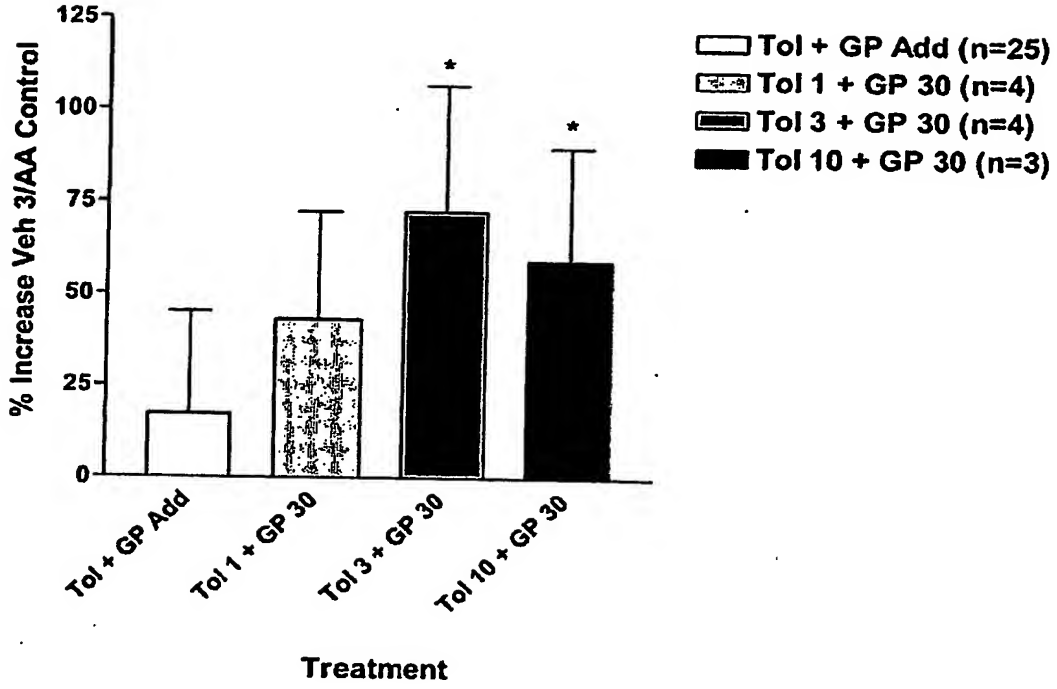


Figure 10

Statistical Analysis of Synergy between Tolterodine and Gabapentin Effects on Reversing Acetic Acid Irritation as Measured by Decreased Bladder Capacity using Calculated Theoretical Additive Population: Dose 1



Data Expressed as Mean ± SD
* P<0.05 by Mann Whitney t Test

Conclusions

While tolterodine alone had no effect on bladder capacity in the acetic acid irritated model and gabapentin alone was capable of partially reversing the reduction in bladder capacity, the combination of the two drugs at below an effective dose of gabapentin (30 mg/kg) and at the medium and high ineffective doses of tolterodine (3 and 10 mg/kg, respectively) proved to be synergistic.

Example 3 – Gabapentin and Solifenacin

The objective of this study was to determine the effect of combining solifenacin, a musculotropic drug, with gabapentin, a neurotropic drug and subunit calcium channel modulator, on the ability to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder.

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with solifenacin alone (n=4), gabapentin alone (n=11), and respective dose–matched combinations of solifenacin and gabapentin (n=13). Cumulative dose-response protocols were utilized with half log increments for all studies. A total of 28 rats, all of which demonstrated irritation indices of between 50 and 90% prior to drug administration initiation, were utilized for generating this report.

The current data indicate that combining solifenacin and gabapentin results in higher efficacy than would be expected from simple additive effects. Although the inventors do not wish to be bound by any particular mechanism or mechanisms of action, the synergistic nature of this interaction is hypothesized to arise both from the difference of each drug's primary target, smooth muscle versus neuronal for solifenacin and gabapentin, respectively, as well as from the subunit calcium channel blocking capabilities at the level of the primary afferents of solifenacin and gabapentin, respectively.

Methods

Drugs and Preparation: Gabapentin was purchased from commercial suppliers and solifenacin was synthesized by Evotec OAI. Pilot studies enabled determination of

effective dose ranges for a 3 point cumulative dose-response for each drug for the initial studies. Drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for solifenacin and 30, 100 and 300 mg/ml for gabapentin. Synergy studies utilized these doses in sequential combination (e.g. 1 mg/ml solifenacin with 30 mg/ml gabapentin for Dose 1, 3 mg/ml solifenacin with 100 mg/ml gabapentin for Dose 2, and 10 mg/kg solifenacin with 300 mg/kg gabapentin). Animals were dosed by (volume of injection in ml) = (body weight in kg * 1.5).

Acute Anesthetized In Vivo Model:

Animal Preparation: Female rats (250-275 g BW) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. A heparinized (100 units/ml) saline-filled carotid catheter (PE-50) was also inserted for blood pressure monitoring. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording and secured by ligation. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design - Dilute Acetic Acid Model: Saline was continuously infused at a rate of 0.055 ml/min via the bladder filling catheter for 60-90 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a 0.25% acetic acid solution (AA) in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle (referred to as AA/Veh 3), and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was

emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity caused by the continuous irritation protocol and subsequent intravesical drug administration. Body temperature was maintained at 37 C with a heating pad.

Data Analysis

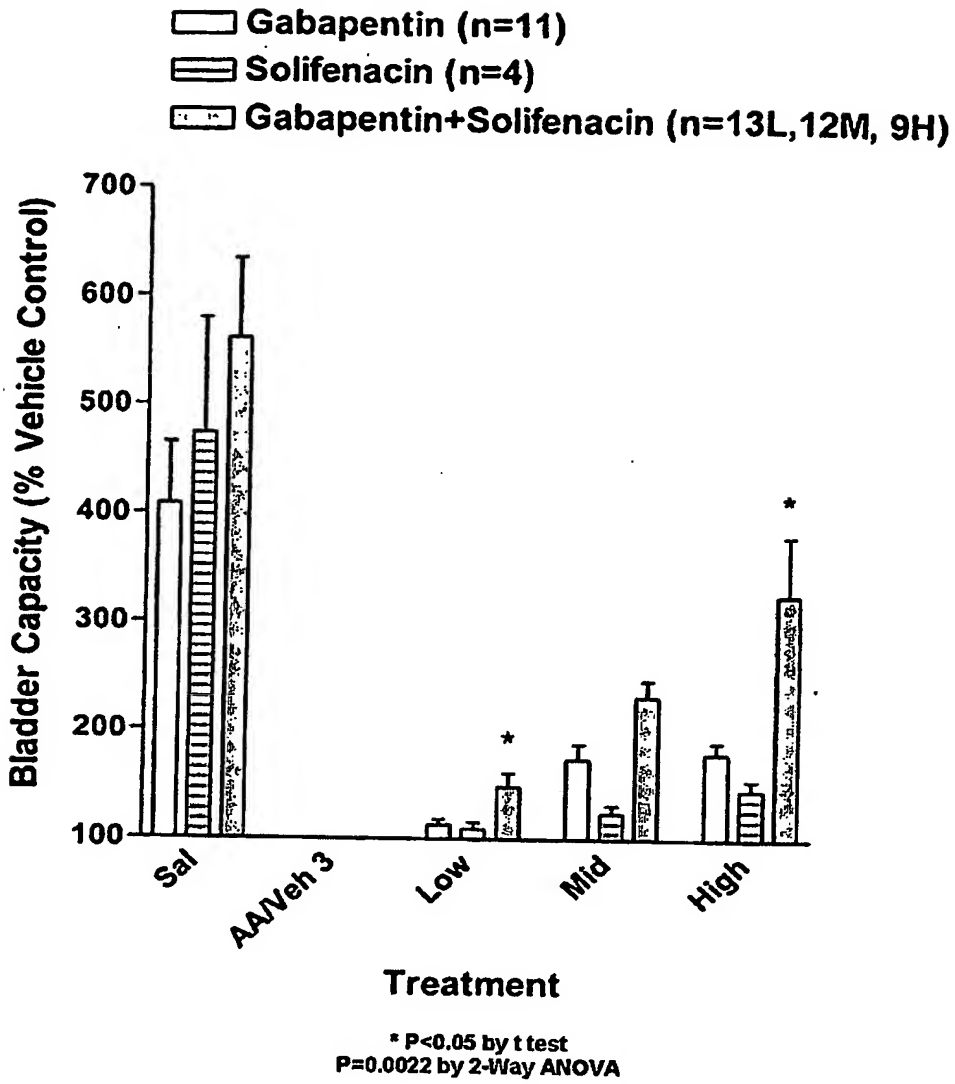
Bladder capacity was estimated by multiplying the flow rate by the number of minutes to first micturition contraction following initiaition of single filling cystometry. For the purposes of statistically proving synergy using all of the data simultaneously, bladder capacity data for each animal were normalized to AA/Veh 3, and the change from AA/Veh 3 was used as the measure of efficacy. A strategy was devised that utilized the data from the solifenacin and gabapentin alone experiments to create a theoretical population of additive results that can be generated from these data for each dose (low, mid and high) and these were compared by t-test (individual doses) and by 2-Way ANOVA (for all doses) to the actual combination drug data. For these purposes, the means and standard deviations of each individual treatment's "dose-matched" (low, middle, and high) responses were added together to estimate the mean and standard deviation of the theoretical additive population for which to compare to the actual data obtained from the combination experiments. The theoretical additive effect population N $= (N_{Solifenacin} + N_{Gabapentin}) - 2$. $P<0.050$ was considered significant. Only rats that showed between a 50-90% reduction in bladder capacity at the third vehicle measurement when compared to pre-irritation saline control values were utilized for numerical analyses.

Results

Individual t-tests (performed as described above) demonstrated that the mean for the combination was greater than the additive means of the individual compounds at both the low and high combination doses ($P<0.05$; Figure 1). Moreover, the 2-Way ANOVA across all doses revealed a significant synergistic effect (i.e., that was greater than additive) between solifenacin and gabapentin ($P<0.0022$).

Figure Legend

Figure 11: Graphic depiction of the effect of cumulative increasing doses of solifenacin (n=4), gabapentin (n=11) and their matched combinations (e.g. Dose 1 for the combination was 30 mg/kg gabapentin and 1 mg/kg solifenacin; n=13, 12 and 9 for Low, Mid and High doses, respectively). Note that the Y-axis has been set to a minimum of 100%, visually subtracting the AA/Veh 3 baseline). In addition, note that both drugs alone had modest abilities to reverse the reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid. Both by individual dose comparison t tests at the Low and High doses ($P<0.05$) and by 2-Way ANOVA for overall effect ($P<0.0022$), statistical analyses revealed that the combination of the two drugs produced a synergistic effect that was greater than what would be expected if the effects were additive. Data are presented as Mean ± SEM.



Conclusions

While solifenacin alone showed modest ability to reverse the reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid, statistical analyses revealed that the combination of the two drugs produced a synergistic effect that was greater than what would be expected if the effects were additive.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following embodiments are encompassed by the present invention:

1. A pharmaceutical composition comprising an $\alpha_2\delta$ subunit calcium channel modulator and an antimuscarinic in an amount sufficient to produce a synergistic effect.

2. The pharmaceutical composition of claim 1 wherein said antimuscarinic is oxybutynin.

3. The pharmaceutical composition of claim 1 wherein said $\alpha_2\delta$ subunit calcium channel modulator is a GABA analog.

4. The pharmaceutical composition of claim 3 wherein said GABA analog is gabapentin.

5. The pharmaceutical composition of claim 4 wherein said antimuscarinic is oxybutynin.

6. A pharmaceutical composition comprising gabapentin and oxybutynin or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof in an amount sufficient to treat lower urinary tract disorders.

7. A pharmaceutical composition comprising gabapentin and oxybutynin or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof wherein said gabapentin is present in an amount from about 600 mg to about 2400 mg, and wherein said oxybutynin is present in an amount less than about 5 mg.

8. A pharmaceutical composition comprising gabapentin and oxybutynin or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof, wherein said gabapentin and oxybutynin are present in a ratio based on a fraction of their

respective ED_{50} values, and wherein said ratio is from about 1:1 to about 300:1 or from about 1:1 to about 1:300, respectively.

9. A combination comprising amounts of gabapentin and oxybutynin or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof in a weight/weight ratio of from 1:1 to about 300:1 or from about 1:1 to about 1:300, respectively.

10. A method for treating lower urinary tract disorders, which comprises administering to an individual in need thereof a therapeutically effective amount of a first component that is an $\alpha_2\delta$ subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in combination with a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof.

11. The method of embodiment 10, wherein the lower urinary tract disorder is a painful lower urinary tract disorder.

12. The method of embodiment 10, wherein the lower urinary tract disorder is a non-painful lower urinary tract disorder.

13. The method of embodiment 12, wherein the non-painful lower urinary tract disorder is non-painful overactive bladder.

14. The method of embodiment 10, wherein the lower urinary tract disorder is selected from the group consisting of overactive bladder, prostatitis, prostadynia, interstitial cystitis, benign prostatic hyperplasia, and spastic bladder.

15. The method of embodiment 10, wherein the active agents are contained within a pharmaceutical formulation.

16. The method of embodiment 15, wherein the pharmaceutical formulation is a unit dosage form.

17. The method of embodiment 10, wherein the $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. Gabapentin and derivatives and analogs thereof;

b. Pregabalin and derivatives and analogs thereof;

c. GABA analogs as described in U.S. Pat. No. 4,024,175 and derivatives and analogs thereof;

d. GABA analogs as described in U.S. Pat. No. 5,563,175 and derivatives and analogs thereof;

e. GABA analogs as described in U.S. Patent No. 6,316,638 and derivatives and analogs thereof;

f. GABA analogs as described in PCT Publication No. WO 93/23383 and derivatives and analogs thereof;

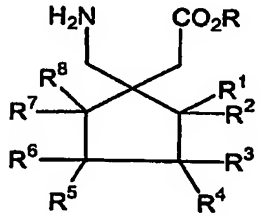
g. GABA analogs as described in Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845 and derivatives and analogs thereof;

h. GABA analogs as described in Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177 and derivatives and analogs thereof;

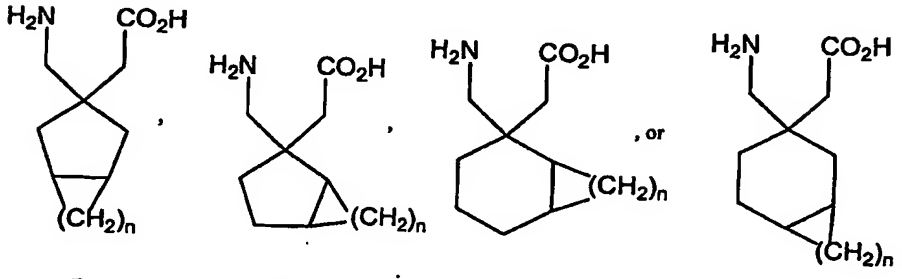
i. Amino acid compounds as described in U.S. Application No. 20020111338 and derivatives and analogs thereof;

j. Cyclic amino acid compounds as disclosed in PCT Publication No. WO 99/08670 and derivatives and analogs thereof;

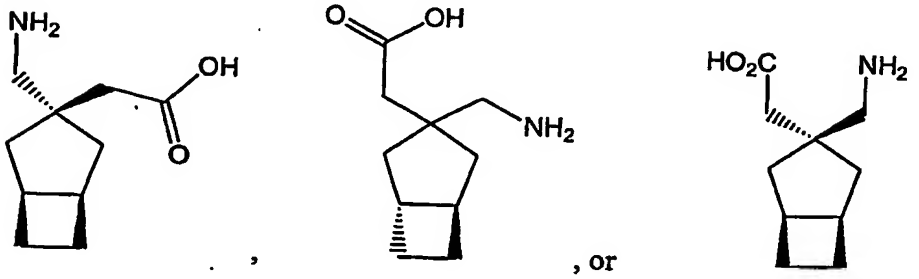
k. Cyclic amino acids (illustrated below) as disclosed in PCT Publication No. WO99/21824 and derivatives and analogs thereof;



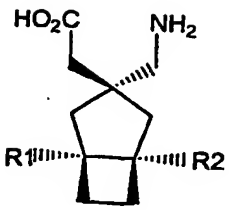
l. Bicyclic amino acids (illustrated below) as disclosed in published U.S. Patent Application No. 60/160725; and



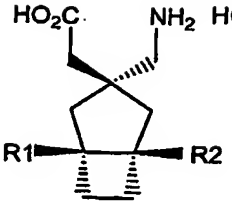
I II III IV



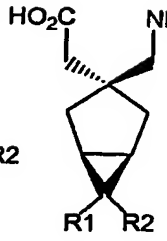
m. Bicyclic amino acid analogs (illustrated below) as disclosed in UK Patent Application GB 2 374 595 and derivatives and analogs thereof.



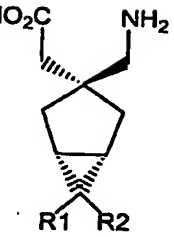
(I)



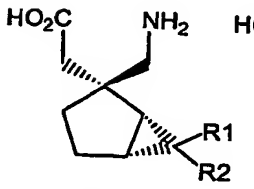
(II)



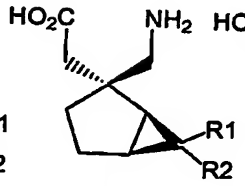
(III)



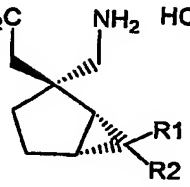
(IV)



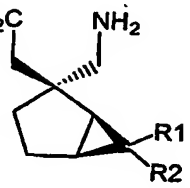
(V)



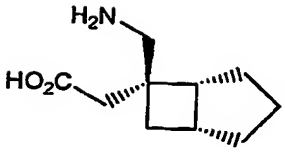
(VI)



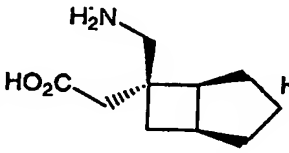
(VII)



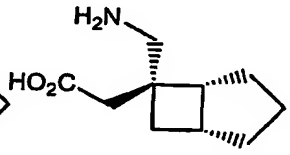
(VIII)



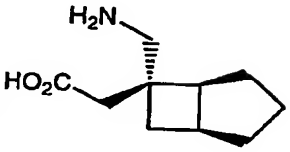
(IX)



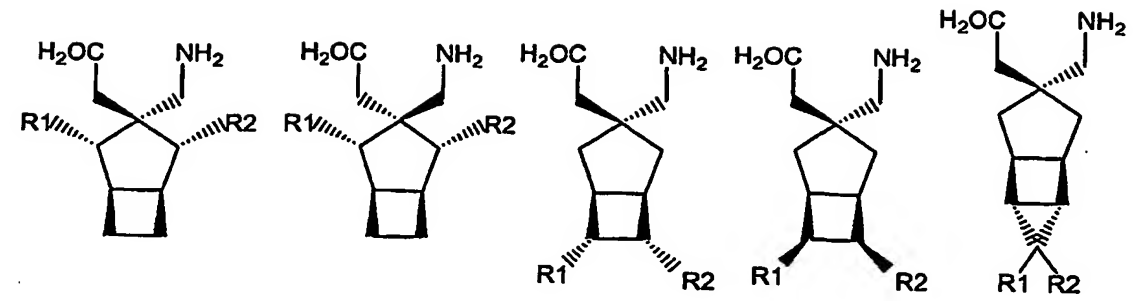
(X)



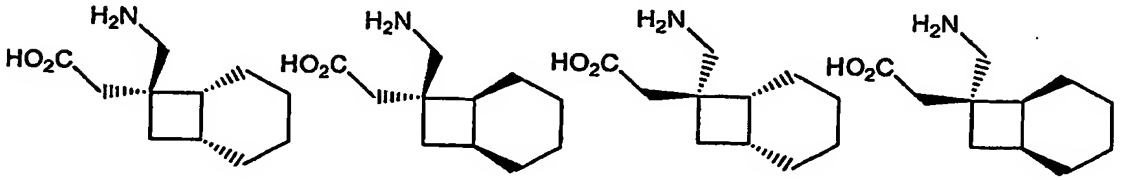
(XI)



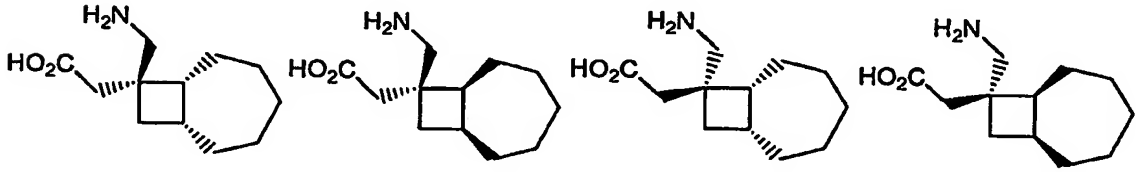
(XII)



(XIII) (XIV) (XV) (XVI) (XVII)



(XVIII) (XIX) (XX) (XXI)



(XXI) (XXII) (XXIII) (XXIV)

18. The method of embodiment 10, wherein said smooth muscle modulator is selected from the group consisting of: antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

19. The method of embodiment 18, wherein said smooth muscle modulator is an antimuscarinic.

20. The method of embodiment 19, wherein the antimuscarinic is selected from the group consisting of:

a. Darifenacin (Daryon®);
b. Solifenacin;
c. YM-905 (solifenacin succinate);
d.
e. Oxybutynin (Ditropan®);
f. S-Oxybutynin;
g. N-desethyl-oxybutynin;
h. tolterodine (Detrol®);
i.
j. Propiverine (Detrunorm®);
k. Propantheline bromide (Pro-Banthine®);
l. Hyoscyamine sulfate (Levsin®, Cystospaz®);
m. Dicyclomine hydrochloride (Bentyl®);
n. Flavoxate hydrochloride (Urispas®);
o. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
p. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;
q. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;
r. alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol proprionate;
s. 1-methyl-4-piperidyl diphenylpropoxyacetate;
t. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;
u. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;
v. pirenzipine;
w. methoctramine;
x. 4-diphenylacetoxy-N-methyl piperidine methiodide;
y. tropicamide;
z. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and

y. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5 hydroxymethylphenyl)-3-phenylpropanamine).

21. The method of embodiment 18, wherein said smooth muscle modulator is a β3 adrenergic agonist.

22. The method of embodiment 21, wherein the β3 adrenergic agonist is selected from the group consisting of:

a. TT-138 and phenylethanolamine compounds;
b. FR-149174 and propanolamine derivatives;
c. KUC-7483;
d. 4'-hydroxynorephedrine derivatives;
e. 2-amino-1-phenylethanol compounds;
f. GS 332;
g. BRL-37,344;
h. BRL-26830A;
i. CGP 12177;
j. CL 316243;
k. ICI 215,001 HCl;
l. ZD 7114 HCl;
m. Pindolol;
n. (*S*)-(-)-Pindolol;
o. SR 59230A HCl; and
p. SR 58611.

23. The method of embodiment 18, wherein said smooth muscle modulator is a spasmolytic.

24. The method of embodiment 23, wherein the spasmolytic is selected from the group consisting of:

a. α-α-diphenylacetic acid-4-(N-methyl-piperidyl) esters;

b. Dioxazocine derivatives;

c. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylnorscopine ethers;

d. Quaternary salts of dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones;

e. Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts;

f. Triazinones;

g. Piperazino-pyrimidines;

h. Aralkylamino carboxylic acids; and

i. Aralkylamino sulfones.

25. The method of embodiment 18, wherein said smooth muscle modulator is a neurokinin receptor antagonist.

26. The method of embodiment 25, wherein the neurokinin receptor antagonist is selected from the group consisting of: RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877 and TAK-637.

27. The method of embodiment 18, wherein said smooth muscle modulator is a bradykinin receptor antagonist.

28. The method of embodiment 27, wherein the bradykinin receptor antagonist is selected from the group consisting of: des-arg^{10}HOE 140; des-Arg^{9}bradykinin; NPC 349; NPC 567; HOE 140; MEN11270; Icatibant; FR173567; and WIN 64338.

29. The method of embodiment 18, wherein said smooth muscle modulator is a nitric oxide donor.

30. The method of embodiment 29, wherein the nitric oxide donor is selected from the group consisting of:

a. Nitroglycerin;
b. Sodium nitroprusside;
c. FK 409 (NOR-3);
d. FR 144420 (NOR-4);
e. 3-morpholinosydnonimine;
f. Linsidomine chlorohydrate ("SIN-1");
g. S-nitroso-N-acetylpenicillamine ("SNAP");
h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
i. NCX 4016 (available from NicOx S.A.);
j. NCX 701 (available from NicOx S.A.);
k. NCX 1022 (available from NicOx S.A.);
l. HCT 1026 (available from NicOx S.A.);
m. NCX 1015 (available from NicOx S.A.);
n. NCX 950 (available from NicOx S.A.);
o. NCX 1000 (available from NicOx S.A.);
p. NCX 1020 (available from NicOx S.A.);
q. AZD 4717 (available from NicOx S.A.);
r. NCX 1510/NCX 1512 (available from NicOx S.A.);
s. NCX 2216 (available from NicOx S.A.);
t. NCX 4040 (available from NicOx S.A.);
u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;
v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;
w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;
x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;
y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;
z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;
aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;
bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;
cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;

dd. Nitric oxide donors as disclosed in U.S. Patent No.5,714,511;

ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911; and

ff. Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

31. The method of embodiment 10, wherein the active agents are administered on an as-needed basis.

32. The method of embodiment 31, wherein the active agents are administered prior to commencement of an activity wherein suppression of the symptoms of overactive bladder would be desirable.

33. The method of embodiment 15, wherein the formulation is a controlled release dosage form.

34. The method of embodiment 33, wherein the formulation is a delayed release dosage form.

35. The method of embodiment 33, wherein the formulation is a sustained release dosage form.

36. The method of embodiment 34, wherein the formulation is a sustained release dosage form.

37. The method of embodiment 35, wherein the sustained release dosage form provides drug release over a time period of from about 6 hours to about 8 hours.

38. The method of embodiment 10, wherein the active agents are administered orally.

39. The method of embodiment 15, wherein the active agents are administered orally.

40. The method of embodiment 39, wherein the pharmaceutical formulation is selected from the group consisting of tablets, capsules, caplets, solutions, suspensions, syrups, granules, beads, powders and pellets.

41. The method of embodiment 40, wherein the pharmaceutical formulation comprises a tablet.

42. The method of embodiment 40, wherein the pharmaceutical formulation comprises a capsule.

43. The method of embodiment 10, wherein the active agents are administered transmucosally.

44. The method of embodiment 43, wherein the active agents are administered sublingually.

45. The method of embodiment 43, wherein the active agents are administered buccally.

46. The method of embodiment 43, wherein the active agents are administered intranasally.

47. The method of embodiment 43, wherein the active agents are administered transurethrally.

48. The method of embodiment 43, wherein the active agents are administered rectally.

49. The method of embodiment 43, wherein the active agents are administered by inhalation.

50. The method of embodiment 10, wherein the active ingredient is administered intravesically.

51. The method of embodiment 10, wherein the active agents are administered topically.

52. The method of embodiment 10, wherein the active agents are administered transdermally.

53. The method of embodiment 10, wherein the active agents are administered parenterally.

54. The method of embodiment 10, wherein the active agents are administered intrathecally.

55. The method of embodiment 15, wherein the active agents are administered intrathecally.

56. The method of embodiment 15, wherein the active agents are administered by a route of administration selected from the group consisting of: vaginally and perivaginally.

57. The method of embodiment 56, wherein the formulation is selected from the group consisting of vaginal suppositories, creams, ointments, liquid formulations, pessaries, tampons, gels, pastes, foams and sprays.

58. The method of embodiment 10, wherein the individual in need thereof is an individual suffering from a spinal cord injury.

59. The method of embodiment 58, wherein the lower urinary tract disorder is spastic bladder.

60. A pharmaceutical formulation for treating lower urinary tract disorders and adapted for transmucosal drug administration, comprising a therapeutically effective amount of a first component that is an $\alpha_2\delta$ subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite therèof in combination with a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, and a carrier suitable for transmucosal drug delivery buccally, sublingually, intranasally, rectally, or by inhalation.

61. The formulation of embodiment 60, wherein the lower urinary tract disorder is a painful lower urinary tract disorder.

62. The formulation of embodiment 50, wherein the lower urinary tract disorder is a non-painful lower urinary tract disorder.

63. The formulation of embodiment 62, wherein the non-painful lower urinary tract disorder is non-painful overactive bladder.

64. The formulation of embodiment 60, wherein the lower urinary tract disorder is selected from the group consisting of overactive bladder, prostatitis, prostadynia, interstitial cystitis, benign prostatic hyperplasia, and spastic bladder.

65. The formulation of embodiment 60, comprising a solid dosage form for application to the buccal mucosa, and wherein the carrier is suitable for buccal drug delivery.

66. The formulation of embodiment 65, wherein the carrier is a hydrolyzable polymer.

67. The formulation of embodiment 65, wherein the dosage form further comprises an adhesive suitable for affixing the dosage form to the buccal mucosa.

68. The formulation of embodiment 60, comprising a dosage form for application to the sublingual mucosa, and wherein the carrier is suitable for sublingual drug delivery.

69. The formulation of embodiment 60, comprising a dosage form for application to the rectal mucosa, and wherein the carrier is suitable for rectal drug delivery.

70. The formulation of embodiment 69, comprising a rectal suppository.

71. The formulation of embodiment 60, comprising a dosage form suitable for inhalation.

72. The formulation of embodiment 71, comprising a liquid.

73. The formulation of embodiment 71, comprising a dry powder.

74. The formulation of embodiment 71, comprising an aerosol composition.

75. The formulation of embodiment 60, wherein the active agents are administered by a route of administration selected from the group consisting of: vaginally and perivaginally.

76. The formulation of embodiment 75, wherein the formulation is selected from the group consisting of vaginal suppositories, creams, ointments, liquid formulations, pessaries, tampons, gels, pastes, foams and sprays.

77. The formulation of embodiment 60, wherein the $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. Gabapentin and derivatives and analogs thereof;

b. Pregabalin and derivatives and analogs thereof;

c. GABA analogs as described in U.S. Pat. No. 4,024,175 and derivatives and analogs thereof;

d. GABA analogs as described in U.S. Pat. No. 5,563,175 and derivatives and analogs thereof;

e. GABA analogs as described in U.S. Patent No. 6,316,638 and derivatives and analogs thereof;

f. GABA analogs as described in PCT Publication No. WO 93/23383 and derivatives and analogs thereof;

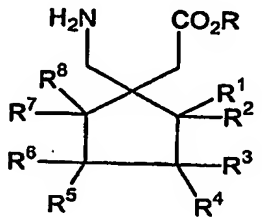
g. GABA analogs as described in Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845 and derivatives and analogs thereof;

h. GABA analogs as described in Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177 and derivatives and analogs thereof;

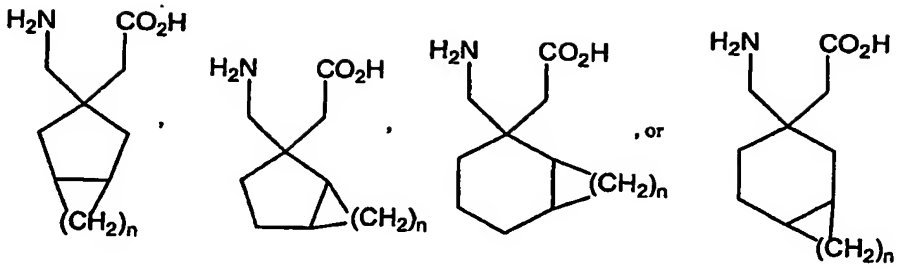
i. Amino acid compounds as described in U.S. Application No. 20020111338 and derivatives and analogs thereof;

j. Cyclic amino acid compounds as disclosed in PCT Publication No. WO 99/08670 and derivatives and analogs thereof;

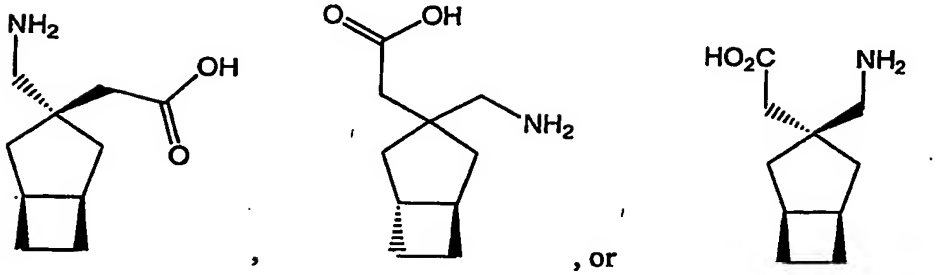
k. Cyclic amino acids (illustrated below) as disclosed in PCT Publication No. WO99/21824 and derivatives and analogs thereof;



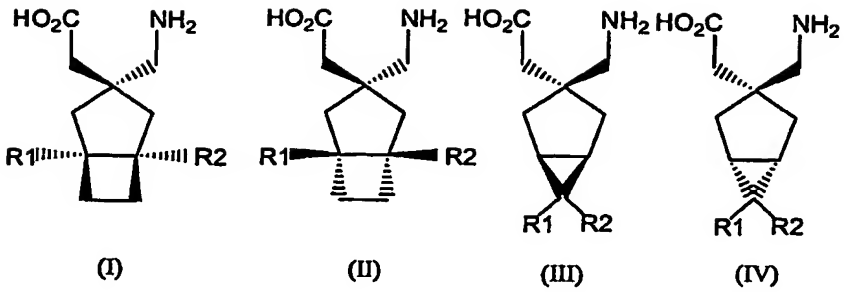
l. Bicyclic amino acids (illustrated below) as disclosed in published U.S. Patent Application No. 60/160725; and



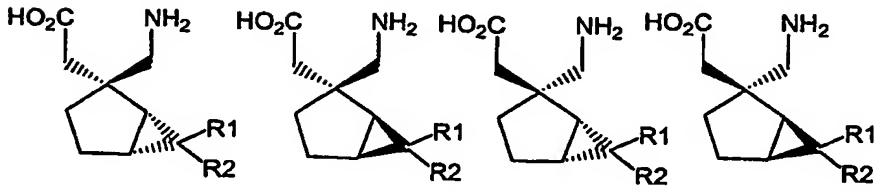
I II III IV



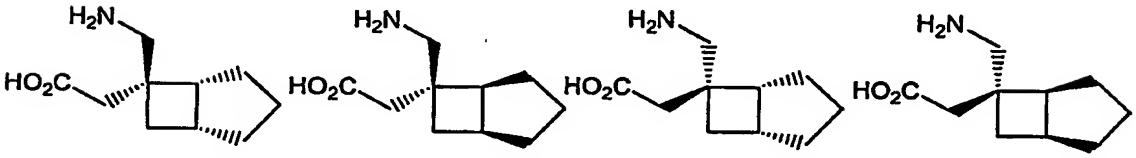
m. Bicyclic amino acid analogs (illustrated below) as disclosed in UK Patent Application GB 2 374 595 and derivatives and analogs thereof.



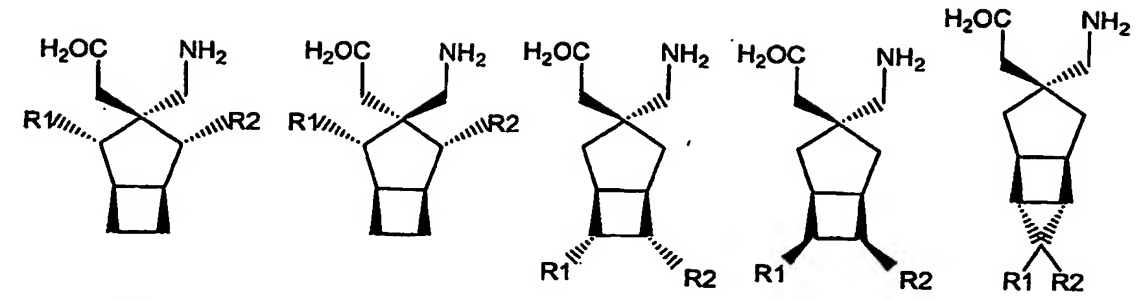
(I) (II) (III) (IV)



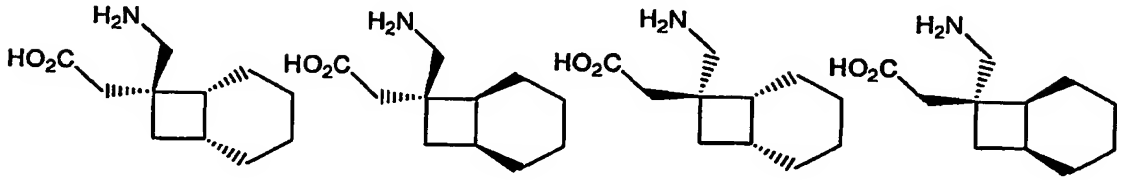
(V) (VI) (VII) (VIII)



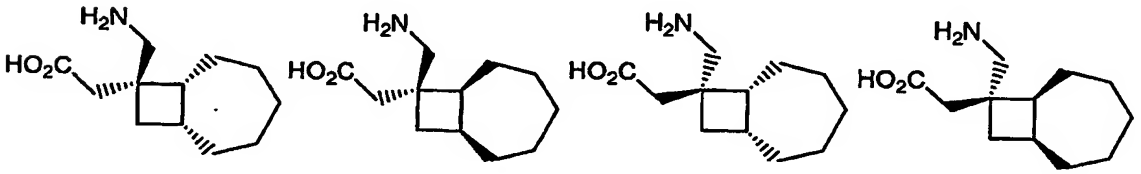
(IX) (X) (XI) (XII)



(XIII) (XIV) (XV) (XVI) (XVII)



(XVIII) (XIX) (XX) (XXI)



(XXI) (XXII) (XXIII) (XXIV)

78. The formulation of embodiment 60, wherein said smooth muscle modulator is selected from the group consisting of: antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

79. The formulation of embodiment 78, wherein said smooth muscle modulator is an antimuscarinic.

80. The formulation of embodiment 79, wherein the antimuscarinic is selected from the group consisting of:

a. Darifenacin (Daryon®);
b. Solifenacin;
c. YM-905 (solifenacin succinate);
d. Solifenacin monohydrochloride;
e. Oxybutynin (Ditropan®);
f. S-Oxybutynin;
g. N-desethyl-oxybutynin;
h. tolterodine (Detrol®);
i. Propiverine (Detrunorm®);
j. Propantheline bromide (Pro-Banthine®);
k. Hyoscyamine sulfate (Levsin®, Cystospaz®);
l. Dicyclomine hydrochloride (Bentyl®);
m. Flavoxate hydrochloride (Urispas®);
n. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
o. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;
p. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;
q. alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol proprionate;
r. 1-methyl-4-piperidyl diphenylpropoxyacetate;
s. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;
t. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;
u. pirenzipine;
v. methoctramine;
w. 4-diphenylacetoxy-N-methyl piperidine methiodide;
x. tropicamide;
y. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and

y. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine).

81. The formulation of embodiment 78, wherein said smooth muscle modulator is a β3 adrenergic agonist.

82. The formulation of embodiment 81, wherein the β3 adrenergic agonist is selected from the group consisting of:

a. TT-138 and phenylethanolamine compounds;
b. FR-149174 and propanolamine derivatives;
c. KUC-7483;
d. 4'-hydroxynorephedrine derivatives;
e. 2-amino-1-phenylethanol compounds;
f. GS 332;
g. BRL-37,344;
h. BRL-26830A;
i. CGP 12177;
j. CL 316243;
k. ICI 215,001 HCl;
l. ZD 7114 HCl;
m. Pindolol;
n. (*S*)-(-)-Pindolol;
o. SR 59230A HCl; and
p. SR 58611.

83. The formulation of embodiment 78, wherein said smooth muscle modulator is a spasmolytic.

84. The formulation of embodiment 83, wherein the spasmolytic is selected from the group consisting of:

a. α-α-diphenylacetic acid-4-(N-methyl-piperidyl) esters;

b. Dioxazocine derivatives;

c. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylnorscopine ethers;

d. Quaternary salts of dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones;

e. Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts;

f. Triazinones;

g. Piperazino-pyrimidines;

h. Aralkylamino carboxylic acids; and

i. Aralkylamino sulfones.

85. The formulation of embodiment 78, wherein said smooth muscle modulator is a neurokinin receptor antagonist.

86. The formulation of embodiment 85, wherein the neurokinin receptor antagonist is selected from the group consisting of: RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877 and TAK-637.

87. The formulation of embodiment 78, wherein said smooth muscle modulator is a bradykinin receptor antagonist.

88. The formulation of embodiment 87, wherein the bradykinin receptor antagonist is selected from the group consisting of: des-arg^{10}HOE 140; des-Arg^{9}bradykinin; NPC 349; NPC 567; HOE 140; MEN11270; Icatibant; FR173567; and WIN 64338.

89. The formulation of embodiment 78, wherein said smooth muscle modulator is a nitric oxide donor.

90. The formulation of embodiment 89, wherein the nitric oxide donor is selected from the group consisting of:

a. Nitroglycerin;
b. Sodium nitroprusside;
c. FK 409 (NOR-3);
d. FR 144420 (NOR-4);
e. 3-morpholinosydnonimine;
f. Linsidomine chlorohydrate ("SIN-1");
g. S-nitroso-N-acetylpenicillamine ("SNAP");
h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
i. NCX 4016 (available from NicOx S.A.);
j. NCX 701 (available from NicOx S.A.);
k. NCX 1022 (available from NicOx S.A.);
l. HCT 1026 (available from NicOx S.A.);
m. NCX 1015 (available from NicOx S.A.);
n. NCX 950 (available from NicOx S.A.);
o. NCX 1000 (available from NicOx S.A.);
p. NCX 1020 (available from NicOx S.A.);
q. AZD 4717 (available from NicOx S.A.);
r. NCX 1510/NCX 1512 (available from NicOx S.A.);
s. NCX 2216 (available from NicOx S.A.);
t. NCX 4040 (available from NicOx S.A.);
u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;
v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;
w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;
x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;
y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;
z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;
aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;
bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;
cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;

dd. Nitric oxide donors as disclosed in U.S. Patent No.5,714,511;

ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911; and

ff. Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

91. The formulation of embodiment 60, wherein the formulation is administered to an individual suffering from a spinal cord injury.

92. The formulation of embodiment 91, wherein the lower urinary tract disorder is spastic bladder.

93. A packaged kit for a patient to use in the treatment of lower urinary tract disorders , comprising: a pharmaceutical formulation comprising a therapeutically effective amount of a first component that is an $\alpha_2\delta$ subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in combination with a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof; a container housing the pharmaceutical formulation during storage and prior to administration; and instructions for carrying out drug administration in a manner effective to treat lower urinary tract disorders .

94. The packaged kit of embodiment 93, wherein the pharmaceutical formulation is an oral dosage form containing a unit dosage of a first component that is an $\alpha_2\delta$ subunit calcium channel modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in combination with a unit dosage of a second component that is a smooth muscle modulator or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, the unit dosage being a therapeutically effective dosage for treatment of lower urinary tract disorders .

95. The packaged kit of embodiment 93, wherein the lower urinary tract disorder is a painful lower urinary tract disorder.

96. The packaged kit of embodiment 93, wherein the lower urinary tract disorder is a non-painful lower urinary tract disorder.

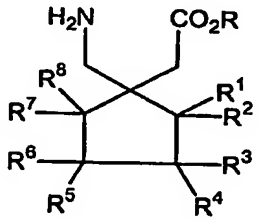
97. The packaged kit of embodiment 96, wherein the non-painful lower urinary tract disorder is non-painful overactive bladder.

98. The packaged kit of embodiment 96, wherein the lower urinary tract disorder is selected from the group consisting of overactive bladder, prostatitis, prostadynia, interstitial cystitis, benign prostatic hyperplasia, and spastic bladder.

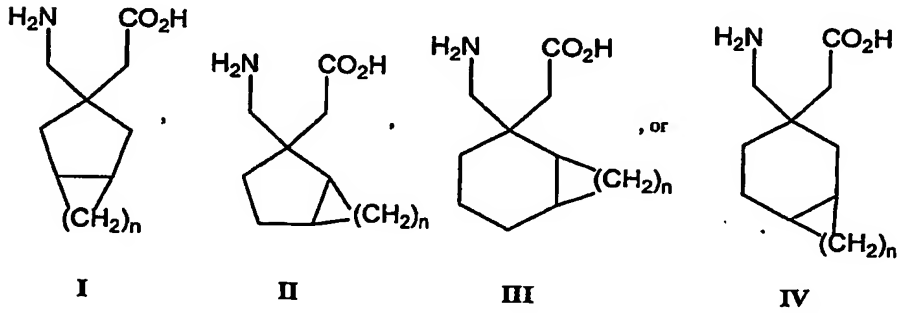
99. The packaged kit of embodiment 93, wherein the $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. Gabapentin and derivatives and analogs thereof;
b. Pregabalin and derivatives and analogs thereof;
c. GABA analogs as described in U.S. Pat. No. 4,024,175 and derivatives and analogs thereof;
d. GABA analogs as described in U.S. Pat. No. 5,563,175 and derivatives and analogs thereof;
e. GABA analogs as described in U.S. Patent No. 6,316,638 and derivatives and analogs thereof;
f. GABA analogs as described in PCT Publication No. WO 93/23383 and derivatives and analogs thereof;
g. GABA analogs as described in Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845 and derivatives and analogs thereof;
h. GABA analogs as described in Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177 and derivatives and analogs thereof;
i. Amino acid compounds as described in U.S. Application No. 20020111338 and derivatives and analogs thereof;
j. Cyclic amino acid compounds as disclosed in PCT Publication No. WO 99/08670 and derivatives and analogs thereof;

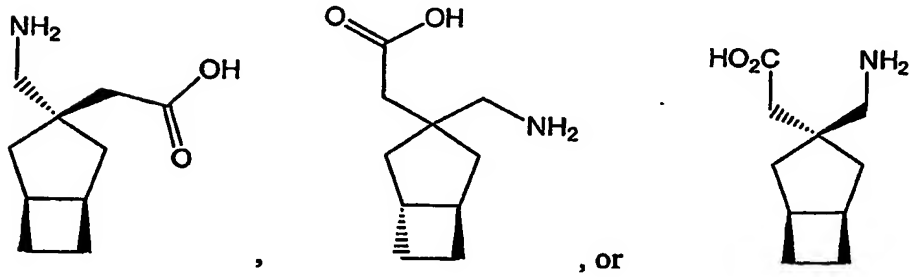
k. Cyclic amino acids (illustrated below) as disclosed in PCT Publication No. WO99/21824 and derivatives and analogs thereof;



l. Bicyclic amino acids (illustrated below) as disclosed in published U.S. Patent Application No. 60/160725; and

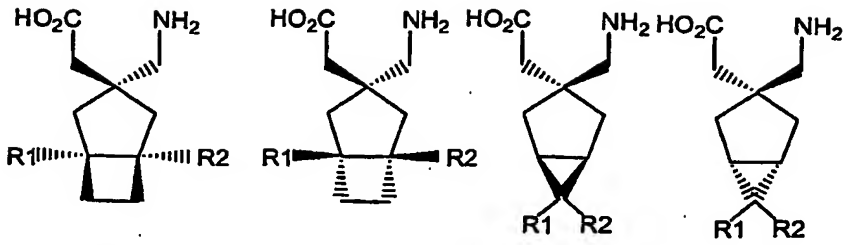


I II III IV

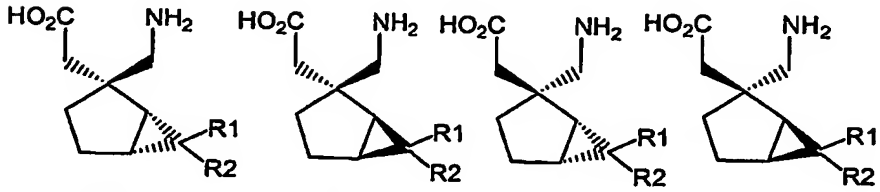


, , or

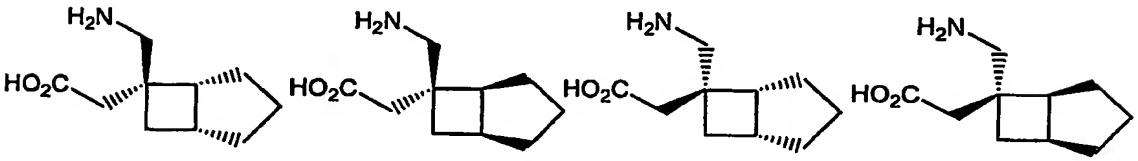
m. Bicyclic amino acid analogs (illustrated below) as disclosed in UK Patent Application GB 2 374 595 and derivatives and analogs thereof.



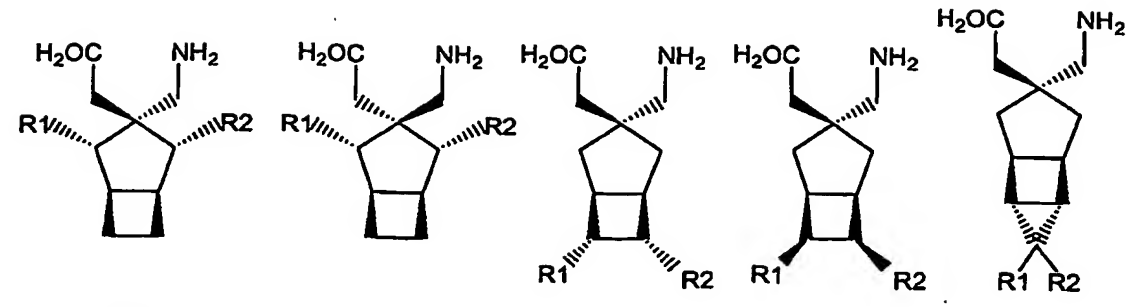
(I) (II) (III) (IV)



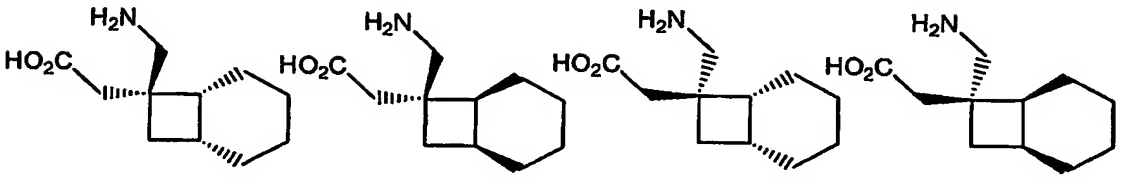
(V) (VI) (VII) (VIII)



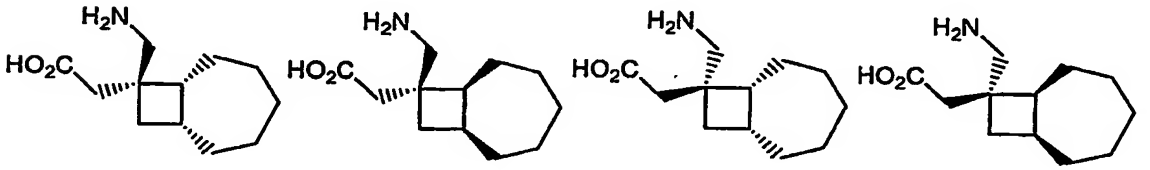
(IX) (X) (XI) (XII)



(XIII) (XIV) (XV) (XVI) (XVII)



(XVIII) (XIX) (XX) (XXI)



(XXI) (XXII) (XXIII) (XXIV)

100. The packaged kit of embodiment 93, wherein said smooth muscle modulator is selected from the group consisting of: antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

101. The packaged kit of embodiment 100, wherein said smooth muscle modulator is an antimuscarinic.

102. The packaged kit of embodiment 101, wherein the antimuscarinic is selected from the group consisting of:

a. Darifenacin (Daryon®);
b. Solifenacin;
c. YM-905 (solifenacin succinate);
d. Solifenacin monohydrochloride;
e. Oxybutynin (Ditropan®);
f. S-Oxybutynin;
g. N-desethyl-oxybutynin;
h. tolterodine (Detrol®);
i.
j. Propiverine (Detrunorm®);
k. Propantheline bromide (Pro-Banthine®);
l. Hyoscyamine sulfate (Levsin®, Cystospaz®);
m. Dicyclomine hydrochloride (Bentyl®);
n. Flavoxate hydrochloride (Urispas®);
o. d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate;
p. (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate;
q. (+)-(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate;
r. alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol proprionate;
s. 1-methyl-4-piperidyl diphenylpropoxyacetate;
t. 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate;
u. 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;
v. pirenzipine;
w. methoctramine;
x. 4-diphenylacetoxy-N-methyl piperidine methiodide;
y. tropicamide;
z. (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; and

y. PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine).

103. The packaged kit of embodiment 100, wherein said smooth muscle modulator is a β3 adrenergic agonist.

104. The packaged kit of embodiment 103, wherein the β3 adrenergic agonist is selected from the group consisting of:

a. TT-138 and phenylethanolamine compounds;
b. FR-149174 and propanolamine derivatives;
c. KUC-7483;
d. 4'-hydroxynorephedrine derivatives;
e. 2-amino-1-phenylethanol compounds;
f. GS 332;
g. BRL-37,344;
h. BRL-26830A;
i. CGP 12177;
j. CL 316243;
k. ICI 215,001 HCl;
l. ZD 7114 HCl;
m. Pindolol;
n. (*S*)-(-)-Pindolol;
o. SR 59230A HCl; and
p. SR 58611.

105. The packaged kit of embodiment 100, wherein said smooth muscle modulator is a spasmolytic.

106. The packaged kit of embodiment 105, wherein the spasmolytic is selected from the group consisting of:

a. α-α-diphenylacetic acid-4-(N-methyl-piperidyl) esters;

b. Dioxazocine derivatives;

c. Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylnorscopine ethers;

d. Quaternary salts of dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones;

e. Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts;

f. Triazinones;

g. Piperazino-pyrimidines;

h. Aralkylamino carboxylic acids; and

i. Aralkylamino sulfones.

107. The packaged kit of embodiment 100, wherein said smooth muscle modulator is a neurokinin receptor antagonist.

108. The packaged kit of embodiment 107, wherein the neurokinin receptor antagonist is selected from the group consisting of: RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877 and TAK-637.

109. The packaged kit of embodiment 100, wherein said smooth muscle modulator is a bradykinin receptor antagonist.

110. The packaged kit of embodiment 109, wherein the bradykinin receptor antagonist is selected from the group consisting of: des-arg^{10}HOE 140; des-Arg^{9}bradykinin; NPC 349; NPC 567; HOE 140; MEN11270; Icatibant; FR173567; and WIN 64338.

111. The packaged kit of embodiment 100, wherein said smooth muscle modulator is a nitric oxide donor.

112. The packaged kit of embodiment 111, wherein the nitric oxide donor is selected from the group consisting of:

a. Nitroglycerin;
b. Sodium nitroprusside;
c. FK 409 (NOR-3);
d. FR 144420 (NOR-4);
e. 3-morpholinosydnonimine;
f. Linsidomine chlorohydrate ("SIN-1");
g. S-nitroso-N-acetylpenicillamine ("SNAP");
h. AZD3582 (CINOD lead compound, available from NicOx S.A.);
i. NCX 4016 (available from NicOx S.A.);
j. NCX 701 (available from NicOx S.A.);
k. NCX 1022 (available from NicOx S.A.);
l. HCT 1026 (available from NicOx S.A.);
m. NCX 1015 (available from NicOx S.A.);
n. NCX 950 (available from NicOx S.A.);
o. NCX 1000 (available from NicOx S.A.);
p. NCX 1020 (available from NicOx S.A.);
q. AZD 4717 (available from NicOx S.A.);
r. NCX 1510/NCX 1512 (available from NicOx S.A.);
s. NCX 2216 (available from NicOx S.A.);
t. NCX 4040 (available from NicOx S.A.);
u. Nitric oxide donors as disclosed in U.S. Patent No. 5,155,137;
v. Nitric oxide donors as disclosed in U.S. Patent No. 5,366,997;
w. Nitric oxide donors as disclosed in U.S. Patent No. 5,405,919;
x. Nitric oxide donors as disclosed in U.S. Patent No. 5,650,442;
y. Nitric oxide donors as disclosed in U.S. Patent No. 5,700,830;
z. Nitric oxide donors as disclosed in U.S. Patent No. 5,632,981;
aa. Nitric oxide donors as disclosed in U.S. Patent No. 6,290,981;
bb. Nitric oxide donors as disclosed in U.S. Patent No. 5,691,423;
cc. Nitric oxide donors as disclosed in U.S. Patent No. 5,721,365;

dd. Nitric oxide donors as disclosed in U.S. Patent No.5,714,511;

ee. Nitric oxide donors as disclosed in U.S. Patent No. 6,511,911; and Nitric oxide donors as disclosed in U.S. Patent No. 5,814,666.

113. The packaged kit of embodiment 93, wherein the pharmaceutical formulation is for administration to an individual suffering from a spinal cord injury.

114. The packaged kit of embodiment 113, wherein the lower urinary tract disorder is spastic bladder.

115. A pharmaceutical formulation comprising oxybutynin or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof in an amount less than about 5 mg together with a pharmaceutically acceptable adjuvant, diluent or carrier.

116. The pharmaceutical formulation of embodiment 115 wherein said oxybutynin or pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof is present in an amount of about 2.5 mg.

117. The pharmaceutical formulation of embodiment 115 wherein said oxybutynin or pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof is present in an amount of about 1.5 mg.

118. A combination product comprising: (A) gabapentin or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof; and (B) oxybutynin or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

119. A combination product as claimed in claim 118 which comprises a pharmaceutical formulation including gabapentin or a pharmaceutically acceptable salt,

ester, amide, prodrug, or active metabolite thereof, and oxybutynin or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

120. A combination product as claimed in claim 118 which comprises a kit of parts comprising components: (a) a pharmaceutical formulation including gabapentin or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and (b) a pharmaceutical formulation including oxybutynin or a pharmaceutically acceptable salt, ester, amide, prodrug, or active metabolite thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier, which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

121. A kit of parts as claimed in claim 120, wherein components (a) and (b) are suitable for sequential, separate and/or simultaneous use in the treatment of lower urinary tract disorders.

122. A method for processing an insurance claim under an insurance policy for treatment of lower urinary tract disorders using an $\alpha_2\delta$ subunit calcium channel modulator and an antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof, wherein said $\alpha_2\delta$ subunit calcium channel modulator and antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof are administered sequentially or concurrently in different compositions, comprising:

a. Receiving notification that treatment using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs or active metabolites thereof will be performed or notification of a prescription;

b. Determining whether said treatment using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable

salts, esters, amides, prodrugs or active metabolites is covered under said insurance policy; and

c. Processing said claim for treatment of said lower urinary tract disorders using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof, including payment, reimbursement, or application against a deductable.

123. The method of claim 122, wherein said $\alpha_2\delta$ subunit calcium channel modulator is gabapentin.

124. The method of claim 123, wherein said antimuscarinic is oxybutynin.

125. The method of claim 122, wherein said antimuscarinic is oxybutynin.

126. A method for processing an insurance claim under an insurance policy for an $\alpha_2\delta$ subunit calcium channel modulator and an antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof used in the treatment of lower urinary tract disorders, wherein said $\alpha_2\delta$ subunit calcium channel modulator and antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof are administered sequentially or concurrently in different compositions, comprising:

a. Receiving notification that treatment using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs or active metabolites thereof will be performed or notification of a prescription;

b. Determining whether said treatment using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs or active metabolites is covered under said insurance policy; and

c. Processing said claim for treatment of said lower urinary tract disorders using said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic or pharmaceutically acceptable salts, esters, amides, prodrugs, or active metabolites thereof, including payment, reimbursement, or application against a deductable.

127. The method of claim 126, wherein said $\alpha_2\delta$ subunit calcium channel modulator is gabapentin.

128. The method of claim 127, wherein said antimuscarinic is oxybutynin.

129. The method of claim 126, wherein said antimuscarinic is oxybutynin.

CLAIMS

What is claimed is:

1. A method for treating lower urinary tract disorders which comprises administering to an individual in need thereof a therapeutically effective amount of a first component that is an $\alpha_2\delta$ subunit calcium channel modulator in combination with a second component that is a smooth muscle modulator, wherein:

a. said lower urinary tract disorder is selected from the group consisting of: overactive bladder, prostatitis, prostadynia, interstitial cystitis, benign prostatic hyperplasia, and spastic bladder;

b. said $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:Gabapentin; pregabalin; GABA analogs as described in U.S. Patent Nos. 4,024,175; 5,563,175; 6,316,638; GABA analogs as described in PCT Publication No. WO 93/23383; GABA analogs as described in Bryans *et al.* (1998) *J. Med. Chem.* 41:1838-1845 and Bryans *et al.* (1999) *Med. Res. Rev.* 19:149-177; amino acid compounds as described in U.S. Application No. 20020111338; cyclic amino acid compounds as disclosed in PCT Publication Nos. WO 99/08670 and WO 99/21824; bicyclic amino acids as disclosed in published U.S. Patent Application No. 60/160725; bicyclic amino acid analogs as disclosed in UK Patent Application GB 2 374 595; and derivatives and analogs thereof; and

c. said smooth muscle modulator is selected from the group consisting of: Darifenacin (Daryon®); solifenacin; YM-905 (solifenacin succinate); solifenacin monohydrochloride; Oxybutynin (Ditropan®); S-Oxybutynin; N-desethyl-oxybutynin; tolterodine (Detrol®); Propiverine (Detrunorm®); Propantheline bromide (Pro-Banthine®); Hyoscyamine sulfate (Levsin®, Cystospaz®); Dicyclomine hydrochloride (Bentyl®); Flavoxate hydrochloride (Urispas®); d,l (racemic) 4- diethylamino-2-butynyl phenylcyclohexylglycolate; (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate; (+)-

(1S,3'R)-quinuclidin-3'-yl 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monosuccinate; alpha(+)-4-(Dimethylamino)-3-methyl-1,2-diphenyl-2-butanol proprionate; 1-methyl-4-piperidyl diphenylpropoxyacetate; 3"-hydroxyspiro[1"H,5"H-nortropane-8,1'-pyrrolidinium benzilate; 4 amino-piperidine containing compounds as disclosed in Diouf *et al.* (2002) *Bioorg. Med. Chem. Lett.* 12: 2535-9;pirenzipine; methoctramine;4-diphenylacetoxy-N-methyl piperidine methiodide; tropicamide; (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide; PNU-200577 ((R)-N, N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine); TT-138 and phenylethanolamine compounds; FR-149174 and propanolamine derivatives; KUC-7483; 4'-hydroxynorephedrine derivatives; 2-amino-1-phenylethanol compounds; GS 332; BRL-37,344; BRL-26830A; CGP 12177; CL 316243; ICI 215,001 HCl; ZD 7114 HCl; Pindolol; (*S*)-(-)-Pindolol; SR 59230A HCl; SR 58611; α-α-diphenylacetic acid-4-(N-methyl-piperidyl) esters; Dioxazocine derivatives; Quaternary 6,11-dihydro-dibenzo-[b,e]-thiepine-11-N-alkylnorscopine ethers; Quaternary salts of dibenzo[1,4]diazepinones, pyrido-[1,4]benzodiazepinones, pyrido[1,5]benzodiazepinones; Endo-8,8-dialkyl-8-azoniabicyclo (3.2.1) octane-6,7-exo-epoxy-3-alkyl-carboxylate salts; Triazinones; Piperazino-pyrimidines; Aralkylamino carboxylic acids; Aralkylamino sulfones; RP 67580; CP 96,345; SR 48968; MEN 10,627; L 659,877; L 659,877; TAK-637; des-arg^{10}HOE 140; des-Arg^{9}bradykinin; NPC 349; NPC 567; HOE 140; MEN11270; Icatibant; FR173567; WIN 64338; Nitroglycerin; Sodium nitroprusside; FK 409 (NOR-3); FR 144420 (NOR-4); 3-morpholinosydnonimine; Linsidomine chlorohydrate ("SIN-1"); S-nitroso-N-acetylpenicillamine ("SNAP"); AZD3582; NCX 4016; NCX 701; NCX 1022; HCT 1026; NCX 1015; NCX 950; NCX 1000; NCX 1020; AZD 4717; NCX 1510/NCX 1512; NCX 2216; and NCX 4040.

2. A pharmaceutical composition comprising gabapentin and oxybutynin wherein said gabapentin is present in an amount from about 600 mg to about 2400 mg, and wherein said oxybutynin is present in an amount less than about 5 mg.

METHODS FOR TREATING LOWER URINARY TRACT DISORDERS USING $\alpha_2\delta$ SUBUNIT CALCIUM CHANNEL MODULATORS WITH SMOOTH MUSCLE MODULATORS

ABSTRACT OF THE DISCLOSURE

A method is provided for using $\alpha_2\delta$ subunit calcium channel modulators or other compounds that interact with the $\alpha\alpha_2\delta$ calcium channel subunit in combination with one or more compounds with smooth muscle modulatory effects to treat painful and non-painful lower urinary tract disorders in normal and spinal cord injured patients. According to the present invention, $\alpha\alpha_2\delta$ subunit calcium channel modulators include gabapentin, pregabalin, GABA analogs, fused bicyclic or tricyclic amino acid analogs of gabapentin, and amino acid compounds. Compounds with smooth muscle modulatory effects include antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.